BRITISH HEART JOURNAL

Volume XX
1958

LONDON
BRITISH MEDICAL ASSOCIATION
TAVISTOCK SQUARE, W.C.1

EDITOR

MAURICE CAMPBELL

ASSOCIATE EDITOR

K. SHIRLEY SMITH

ASSISTANT EDITORS

IAN HILL G. W. HAYWARD WALLACE BRIGDEN

PATRICK MOUNSEY

EDITORIAL BOARD

C. W. CURTIS BAIN, HARROGATE
D. EVAN BEDFORD, LONDON
JAMES W. BROWN, SHEFFIELD
TERENCE EAST, LONDON
WILLIAM EVANS, LONDON
JOHN MCMICHAEL, F.R.S., LONDON
SIR JOHN PARKINSON, LONDON
J. H. WRIGHT, GLASGOW
EDITOR OF *British Medical Journal*

APPOINTED BY

THE BRITISH CARDIAC SOCIETY

27814

CONTENTS OF VOLUME XX

Number 1

		Page
Assymetrical Hypertrophy of the Heart in Young Adults	By Donald Teare	1
Cardiac Syncope in Atrial Septal Defect	By Cornelio Papp	9
Fibrinolysis in Myocardial Infarction	By Robert Hume	15
The Effects of Acute Cardiac Infarction and of Heparin Therapy on the Lipoproteins	By E. M. M. Besterman	21
The Electrocardiogram in Aortic Stenosis	By Zahira H. Abdin	31
The Electrocardiogram in Pulmonary Embolism	By Robert H. Cutforth and Samuel Oram	41
Auscultation in Patent Ductus Arteriosus: with a Description of Two Fistulæ Simulating Patent Ductus	By Catherine Neill and Patrick Mounsey	61
Restenosis of the Mitral Valve	By J. R. Belcher	76
Coronary Heart Disease in the Presence of Pulmonary Disease	By Arthur J. Thomas	83
Patency of the Ductus Arteriosus in the Newborn Calf and Foal	By E. C. Amoroso, G. S. Dawes, and Joan C. Mott	92
The Natural History of Ventricular Septal Defect	By L. Brotmacher and Maurice Campbell	97
Evaluation of Dye Injection Methods in Congenital Heart Disease	By W. Falholt and J. Fabricius	117
Disappearance of Pathological Q Waves after Cardiac Infarction	By M. P. Pappas	123
Electrocardiographic Diagnosis of Right Ventricular Hypertrophy in Infancy and Childhood	By A. Hollman	129
The National Heart Hospital 1857–1957		137
Case Reports		140
Abstracts of Cardiology		150

Number 2

Observer Variation in Reports on Electrocardiograms	By L. G. Davies	153
The Use of Amyl Nitrite in Differentiating Mitral and Aortic Systolic Murmurs	By John Barlow and John Shillingford	162
The Orthogonal Electrocardiogram in Left Ventricular Hypertrophy	By E. J. Fischmann	167
The Spatial Vectorcardiogram in Hypothermia	By D. Emslie-Smith	175
Anti-Streptolysin O Titre in Rheumatic Carditis	By E. N. Chamberlain, C. A. St. Hill, and S. Cope	183
The Influence of Ventricular Hypertrophy upon the Cardiogram of Anterior Cardiac Infarction	By J. F. Goodwin	191
Digitalis and Intractable Heart Failure	By Evan Fletcher and C. F. Brennan	204
The Vectorcardiogram in Atrial Septal Defect	By Neil A. J. Hamer	215
Noradrenaline Sensitivity in Hypertension measured with a Radioactive Sodium Technique	By R. Moulton, A. G. Spencer, and D. A. Willoughby	224
Simple Method for Estimating Mitral Regurgitation by Dye Dilution Curves	By John Shillingford	229
Circulatory Effects of Changing Position in Mitral Disease	By David Cardus, John Mackinnon, and Geoffrey Wade	233
Serum Glutamic Oxalacetic Transaminase Levels in Diphtheritic Myocarditis	By E. Chesler	244
Thoracolumbar Sympathectomy in Hypertension	By W. E. Parkes	249
Unilateral Rib-Notching from the Collateral Circulation after Division of the Subclavian Artery	By Maurice Campbell	253
Symposium on Congenital Heart Disease		261
Proceedings of the British Cardiac Society		290
Abstracts of Cardiology		294

Number 3

	Page
Heart: 1909–1958	297
Louis Gallavardin	299
Hæmodynamic Consequences of Coronary Heart Disease — By Ottar Müller and Karl Rørvik	302
The Diagnostic Use of an Ear Oximeter in Congenital Heart Disease — By C. R. Woolf, W. Paul, and R. W. Gunton	311
The Diagnosis of Mitral Incompetence from Left Atrial Pressure Curves — By Bertrand G. Wells	321
Clinical and Radiological Aspects of Calcification of the Mitral Region — By Eino Linko and Erkki Sysimetsä	329
Atrial Dissociation — By Mario Gomes Marques	335
Direct Left Atrial Pressure Tracings and the Degree of Mitral Obstruction — By Stanley R. McCampbell	341
Evidence for Pulmonary Vasoconstriction in Man — By Richard Gorlin, Frank B. Clare, and Joseph J. Zuska	346
A Surgical Study of Coarctation of the Aorta — By Rowan Nicks	351
Electrocardiograms with Short P–R Interval and Aberrant QRS Complex — By L. M. Sanghvi and S. N. Misra	357
Ventricular Septal Defect with Pulmonary Stenosis and Aortic Regurgitation — By D. M. Collins, T. East, M. P. Godfrey, P. Harris, and S. Oram	363
The Aortic Systolic Murmur developing with Increasing Age — By D. L. Bruns and L. G. Van Der Hauwaert	370
Ventricular Septal Defect with Pulmonary Stenosis — By L. Brotmacher and Maurice Campbell	379
The Role of Venous Constriction in Circulatory Disorders — By János P. Radó, Endre Gonda, and Erwin Kovács	389
Pulmonary Function in Pulmonary Hypertension — By M. B. McIlroy and G. H. Apthorp	397
The Right Ventricle and the Small Pulmonary Arteries in Coalworkers — By Arthur J. Thomas and W. R. L. James	403
Coronary Artery Catheterization during Thoracic Aortography — By A. M. Johnson and William D. Logan	411
The Electrocardiogram in Progressive Muscular Dystrophy — By G. W. Manning and G. J. Cropp	416
Case Reports	421
Abstracts of Cardiology	436

Number 4

The Orientation of the Heart and the Appearance of its Chambers in the Adult Cadaver — By Robert Walmsley	441
Selective Cine-Angiocardiography with Image Intensification — By Hamish Watson, C. Pickard, K. G. Lowe, and Ian Hill	459
The Correlation Between Various Assessments of Pulmonary Arterial Pressure in Mitral Stenosis — By J. F. Boyd, S. D. Scott, Park and George Smith	466
The Functional and Clinical Anatomy of the Mitral Valve — By J. C. Van Der Spuy	471
Residual Lung Volume in Mitral Disease — By R. Garbagni, P. F. Angelino, A. Brusca, and E. Minetto	479
The Electrocardiogram in Syphilitic Heart Disease — By Geoffrey Storey	483
The Electrocardiogram in Pectus Excavatum — By Jorge Martins de Oliveira, Mohinder P. Sambhi, and Henry Zimmerman	495
Modification of Ventricular Gallop Rhythm Induced by Pooling of Blood in the Extremities — By James J. Leonard, Arnold M. Weissler, and James V. Warren	502
The Aortic Lesion of Ankylosing Spondylitis — By B. M. Ansell, E. G. L. Bywaters, and I. Doniach	507
The Cerebral Blood Flow in Mitral Stenosis and its Response to Carbon Dioxide — By H. A. Dewar and L. A. G. Davidson	516
The Effect of Valvotomy on the Murmurs of Pulmonary and Aortic Stenosis — By Bertrand G. Wells	523
Pulmonary Hypertension in Congenital Heart Disease — By William Evans and D. S. Short	529
Fœtal Paroxysmal Auricular Tachycardia — By C. W. Kesson	552
The Vasoconstrictive Factor in Pulmonary Hypertension — By Paul Wood	557
Case Reports	571
J. G. Emanuel	579
Proceedings of the British Cardiac Society	582
Index	593

ASYMMETRICAL HYPERTROPHY OF THE HEART IN YOUNG ADULTS

BY

DONALD TEARE

From the Department of Pathology, St. George's Hospital

Received January 7, 1957

" Tumours of the heart and pericardium have evoked an extensive literature out of all proportion to their uncommon incidence and their relative unimportance as a cause of clinical heart disease." This opening sentence of Friedberg's chapter on cardiac tumours in *Diseases of the Heart* (Friedberg, 1949) fills a pathologist with diffidence in reporting eight cases that have been seen in the last six years in a series of 16,000 autopsies.

Primary tumours of the heart are undoubtedly a rarity and according to Mahaim (1945) 413 had been recorded up to 1945. There is little justification for recording rarities in young adults unless they have some relation to fitness for military service or confuse the differential diagnosis, particularly of conditions that may respond to cardiac surgery. These eight cases of asymmetrical hypertrophy or benign tumour of the heart have occurred in a large group where sudden death and indeed cardiac incapacity, particularly among men, is rare.

Primary tumours of the heart fall into three categories.

(1) Multiple tumours frequently described as congenital glycogenic tumours of the myocardium, which are often associated with other presumably congenital lesions such as tuberous sclerosis and renal tumours.

(2) Single diffuse tumours or asymmetrical hypertrophy of muscle and connective tissue, which are the subject of this article.

(3) Rare myxomata and sarcomata, occurring mainly in later life and producing a variety of symptoms and pathology.

Since the term rhabdomyoma is now firmly associated with nodular glycogenic tumours of the heart it is simpler to refer to the eight tumours under discussion as hamartomata, though they may in fact lay greater claim to being benign tumours of striped muscle than those of presumed glycogenic origin. In Mahaim's (1945) extensive review, which included 329 cases of primary tumour of the heart, only six are referred to as being diffuse tumours of the myocardium, and it would appear that the tumours discussed in this paper fall into this category.

Batchelor and Maun (1925) in recording one case of multiple tumours of the heart in a child of three days reviewed 62 other reported cases. In 60 cases the lesions were multiple, and of the three other cases, one was recorded as having hepatomegaly, one had congenital tumour of the lung, and one had no congenital abnormality. In Eulinger's (1925) record of 37 cases, seven were single tumours and no other congenital abnormality was found. Browne and Gray (1930) record a case of a child of three months who died following a fit of crying, and there was found a diffuse tumour of the lateral wall of the left ventricle similar to the cases about to be described. Hueper (1935 and 1941) described diffuse tumours in the heart of a negro and in the heart of a guinea-pig. Saphir (1953) used the term rhabdomyoma when writing of nodular glycogenic degeneration and gives no reference to benign tumours of striped muscle. Similarly Adams, Denny-Brown, and Pearson (1953) describe nodular glycogenic tumours when referring to rhabdomyoma of the heart.

Case Histories

Case 1. R. S. In September, 1950, a boy of 14, had had a " blackout " and fallen from his bicycle; two months later he again became dizzy and fell to the ground. In neither attack did he bite his tongue or pass water. He was seen at Wembley Hospital on January 1, 1951. At this time he was found to have a blood pressure of 118/70 mm. Hg, a third heart sound and a soft systolic murmur. There was no history of fits, rheumatic fever, or other significant background. He was advised to lead a normal life, excluding cycling, running, or climbing. It was thought that his attacks were cardiac in origin and not epileptic. On February 20, 1951, he was being chased around the playground of his school, when he suddenly collapsed and was found to be dead on arrival at hospital twenty minutes later.

His heart (Fig. 1) showed a localized and diffuse hypertrophy of the interventricular septum. The hypertrophied muscle had a coarse texture when compared with the lateral wall of the ventricle and the proximity of the hypertrophied area to the mitral valve is well seen in the photograph.

Microscopical examination of a section of the tumour (Fig. 2) shows a bizarre arrangement of bundles of muscle fibres running in divers directions and separated by connective tissue and clefts. The connective tissue tends to break up and interrupt the muscle bundles giving an impression of inefficiency in muscular contraction of the tumour as a whole, while the clefts are lined with endothelium covering sparse elastic tissue which is similar to the structure of the normal endocardium. The individual muscle fibres appear to be mature and there is no suggestion of malignancy; they vary considerably in thickness, but in any particular bundle the fibres are of the same thickness, and show sufficient nuclei to indicate that the fibres have been cut centrally and that the appearance of variation in thickness is not due to a chance tangential section.

FIG. 1.—Case 1. Localized hypertrophy of the interventricular septum.

FIG. 2.—Case 1. Disordered arrangement of muscle bundles with variations in size of individual fibres (H & E × 80).

Case 2. E. C. B., aged 25. Apart from pneumonia and empyema when a child of six, this man had served in the Army and had been fit until the autumn of 1953 when he attended his general practitioner complaining of palpitation. No abnormality was detected on routine physical examination and he did not see his doctor again until November, 1954, when he was found to be in congestive heart failure with engorged neck veins, auricular fibrillation, and a pulse rate of 130 a minute. He refused to rest but agreed to take digoxin. Ten days later his pulse had fallen to 80 a minute and the neck veins were less engorged. While walking home on December 26, 1954, he collapsed on the pavement and was found to be dead on reaching hospital twenty-five minutes later.

His heart (Fig. 3) showed hypertrophy similar to that seen in Case 1, though if anything the enlargement of the interventricular septum was greater. The same coarse texture of the muscle can be seen but there were no clefts. The microscopical picture was one of bizarre arrangement of muscle bundles and hypertrophy of individual muscle fibres.

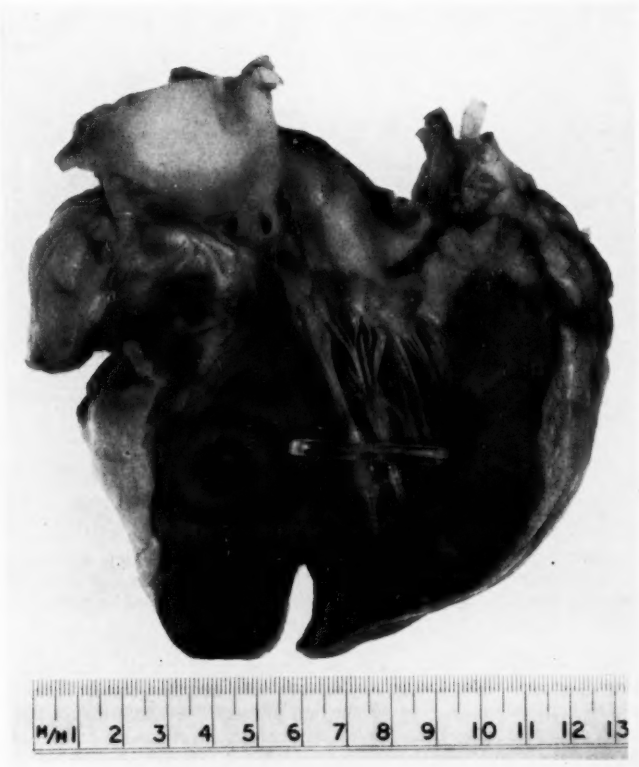


FIG 3.—Case 2. Hypertrophy of the interventricular septum with coarse texture of muscle.

Case 3. G. C., aged 25. This man first came under medical observation when he applied for employment at the Central Medical Establishment, R.A.F., in September, 1953. He claimed to be perfectly fit and free from symptoms. There was no history of rheumatic disease and he had always taken part in games without distress. His heart was in normal rhythm and his blood pressure 130/90. A soft high-pitched systolic murmur just internal to the apex of the heart was heard. It was not accompanied by a thrill and no diastolic murmur was heard even after exercise. His electrocardiogram (Fig. 4) was grossly

abnormal. He was thought to be fit for sedentary occupation, but not for establishment as a civil servant. He continued in his normal health until January 2, 1955, when he awoke from an afternoon sleep, had a series of fits, frothed at the mouth, became rigid, and was dead when a doctor arrived fifteen minutes later.

Post-mortem examination showed him to be well-nourished and muscular. His heart weighed 520 g., this increase being due mainly to an asymmetrical hypertrophy of the interventricular septum and anterior wall of the heart. There was also some hypertrophy of the right atrium and ventricle. The bronchi contained a large quantity of frothy, slightly blood-stained, fluid, which appeared to have come from a terminal œdema of the lungs, and there was a small patch, 3 centimetres in diameter, of recent subarachnoid hæmorrhage over the left parietal cortex. No congenital lesions were found in any other organ.

The coarse and varied arrangement of muscle bundles are well seen in Fig. 5, and the clefts or fissures between muscle bundles were greater than in any other specimen. These endothelial-lined channels communicated with the cavities of both ventricles, but pursued such tortuous and muscle-bound courses as to suggest that there could be no shift of blood from one ventricle to another during systole. The histological picture was identical with the other cases.

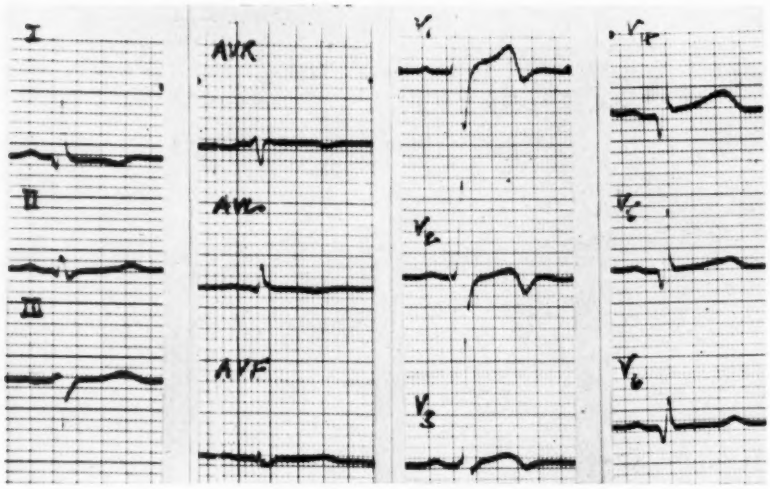


FIG. 4.—Case 3. T inversion in lead I, terminal T inversion in V1, V2, and V3, and abnormally deep Q in V4, V5, and V6. These changes indicate areas of fibrosis or abnormally functioning myocardium in the anterior and lateral walls of the left ventricle.

Case 4. R. W., aged 45 years. This patient at the age of 28 complained of tiredness, pain in the chest, and dyspnœa on exertion. Her doctor at the time told her that she had a murmur and anæmia. These symptoms persisted and at the age of 40 she had an attack of palpitation, which necessitated her admission to hospital for cardiac irregularity where her symptoms responded to quinidine. At the age of 42 digitalization was necessary and valvotomy was considered. In the year prior to her death she had two attacks of breathlessness associated with the coughing up of bloodstained sputum. She slept with two pillows but could walk half a mile before being halted by dyspnœa. There was no history of rheumatic fever but many attacks of tonsillitis followed by scarlatina at the age of 13.

On admission to Guy's Hospital on December 28, 1954, she was found to be fibrillating at the rate of 60 a minute, and her blood pressure was 150/85. At the apex a rumbling diastolic murmur with thrill was found, and a soft aortic diastolic murmur was also heard. Chest X-ray showed the heart to be of mitral shape and an electrocardiogram demonstrated auricular fibrillation with left ventricular preponderance. On January 2, 1955, auscultation revealed a to-and-fro creaking sound, very like a friction rub, over the pulmonary area.

Operation for mitral valvotomy was undertaken on January 4; difficulty was encountered in introducing

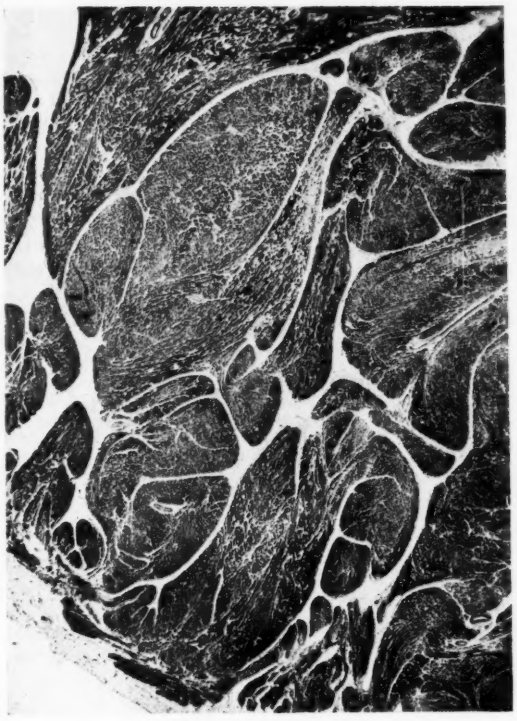


FIG. 5.—Case 3. Numerous large clefts between muscle bundles (H & E×7).

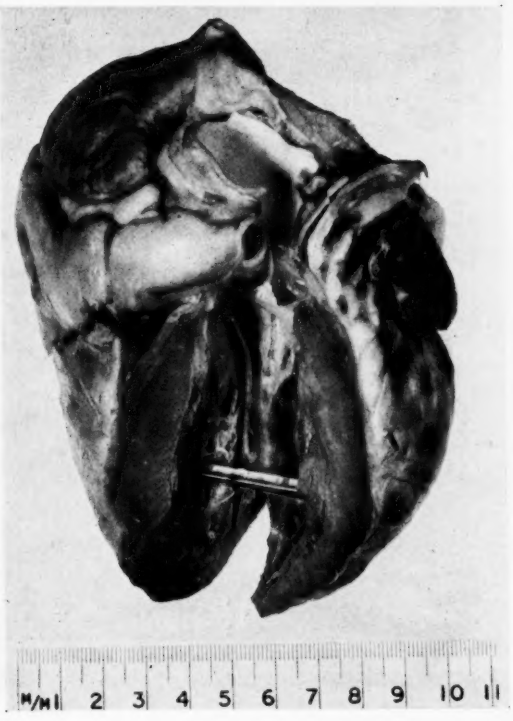


FIG. 6.—Case 4. Hypertrophy of the interventricular septum and anterior wall.

the little finger into the mitral valve and a hard mass, thought to be a calcified thrombus, was noted in the anterior ventricular wall. The mitral valve was split medially and laterally by means of a knife. Some six hours after the operation the blood pressure fell and despite all resuscitative measures death occurred in the early hours of the following morning.

The heart (Fig. 6) showed localized hypertrophy of the interventricular septum and anterior wall with distortion of the mitral valve into the shape of a fishes mouth (Fig. 7). While this distortion and bending of the valve undoubtedly caused narrowing there was no obvious thickening and microscopic section of the hypertrophied interventricular septum was identical with the previous cases.

Case 5. M. F. C., aged 21 years. While running to catch a bus in June, 1956, this young woman suddenly collapsed and was found to be dead on arrival at Wembley Hospital. Her cardiac history could be traced back to the age of eight when following scarlet fever, she had an illness diagnosed as rheumatism which confined her to bed for five months. Following this she attended a special school but at the age of 12 had a further illness with pain in the limbs and palpitation which led to her admittance to the Canadian Hospital, Taplow, where a diagnosis of congenital morbus cordis was made. At the age of 19 she attended Hammersmith Hospital complaining of palpitation and dyspnœa on exertion. She was found to have auricular fibrillation and an electrocardiogram showed right bundle-branch block. Eleven days after admission she reverted to normal rhythm, but two days later had a cerebral embolism. It was thought at this time that the diagnosis rested between Ebstein's syndrome and fibroelastosis. The girl's condition improved steadily and she remained well until the time of her sudden death. An electrocardiogram in September, 1954, showed right atrial hypertrophy and partial right bundle-branch block with questionable right ventricular hypertrophy.

FIG. 7.—Case 4. Distortion of mitral valve.

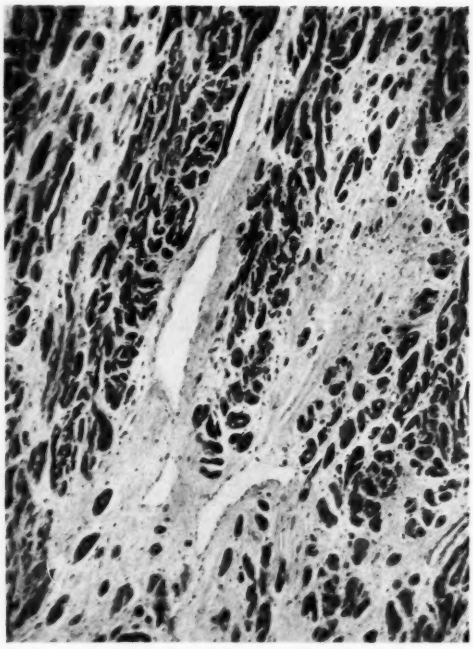


FIG. 8.—Case 5. Extensive fibrosis scattered through muscle bundles (H & E × 80).

At autopsy she was found to be a well-nourished young woman with slight œdema of the ankles. The heart was almost globular in shape weighing 450 g., and both ventricles being hypertrophied. The hypertrophy of the left ventricle was however completely asymmetrical affecting the interventricular septum and anterior wall. The posterior wall appeared to be rather thinner than normal. There was no valvular disease, nor endocarditis, and the coronary arteries and aorta were perfectly healthy. In other organs no congenital abnormalities were found, but an old area of softening was identified in the right temporal lobe of the brain. The liver showed cirrhotic changes indicative of chronic back pressure which may also have been responsible for the right ventricular hypertrophy.

Microscopical examination of the anterior wall of the heart showed bizarre arrangements of muscle bundles, with variation in the individual size of muscle fibres and their nuclei, and a considerable amount of fibrosis (Fig. 8). This fibrosis was found mainly in the centre of muscle bundles and was thought to be ischæmic in origin. A section of the posterior wall of the heart showed a normal arrangement of fibres of constant calibre.

The macroscopic picture of the heart in the three other cases was one of localized hypertrophy of the interventricular septum with a complete absence of vascular, coronary, or aortic disease.

Case 6. A. R., aged 33. This man was thought to have been rejected for military service because of a heart condition but had not consulted a doctor in the six years before his death. He collapsed suddenly on his way to work, and was dead on arrival at hospital. He was found to have a localized hypertrophy of the upper part of the interventricular septum.

Case 7. N. A., aged 28 years. The only history available in this case was one of insomnia for some weeks and he had not consulted a doctor during the 18 months before his death. He collapsed in the street and was dead on arrival at hospital. His heart weighed 390 g. and showed localized hypertrophy of the interventricular septum encroaching on the anterior wall of the left ventricle.

Case 8. J. B., aged 29 years. During a thunderstorm in September, 1951, this man was seen to fall from his pedal cycle and was dead when brought to hospital. The general practitioner was traced but had no record of any visit or consultation in the previous six years. Autopsy failed to reveal the slightest evidence of electric burns or serious injury resulting from the fall. The heart weighed 570 g. and showed localized hypertrophy of the interventricular septum.

Discussion

Of the eight cases described, six occurred in men between the ages of 14 and 35, one in a woman of 20, and one in a woman of 44. Four had had cardiac symptoms, two were discovered to have cardiac lesions on routine examination though symptom free, one had had slight insomnia, and the eighth was symptom free. In three cases palpitation was the most striking early symptom that led to medical examination; all three of these were found to have auricular fibrillation and were in some degree of heart failure, though not completely incapacitated. The young boy presented as an unexplained case of " blackouts " and this symptom was also exhibited by one woman.

In five cases hypertrophy of the right heart indicated some degree of long-standing back pressure, and in three cases there was evidence of chronic venous congestion in the liver. In no case was any other congenital abnormality found.

The macroscopic and microscopic pictures seen in all these cases is virtually the same, differing only in the degree of cleavage between coarse muscle bundles and to a lesser extent in the position of the localized hypertrophy. The overgrowth of muscle may impinge on the ventricular aspect of the mitral valve and lead to symptoms and signs of mitral stenosis so that it is not surprising therefore that Case 4 came to operation for mitral valvotomy.

It appears unlikely that this asymmetrical hypertrophy was traumatic or malignant in origin. The fibrosis evident in certain cases is ischæmic in type and the microscopical picture does not suggest a post-inflammatory condition, although in two cases a history suggestive of acute rheumatism was obtained. It must be admitted that the history available in other cases was so scanty as to be of little significance. The differential diagnosis appears to lie between a congenital and a developmental origin.

There are good reasons for believing that these lesions are in no way associated with congenital glycogenic degenerative tumours in that there was a complete absence of other congenital lesions, in particular cysts of the kidney and tuberous sclerosis, and no history of mental illness or epilepsy in any case: specific stains for the detection of glycogen were constantly negative.

Summary

Eight cases of asymmetrical hypertrophy or muscular hamartoma of the heart are discussed. Seven of these caused sudden death in young adults. The pathological picture is one of bizarre and disorganized arrangement of muscle bundles associated with hypertrophy of individual muscle fibres and their nuclei.

Addendum

On December 13, 1956, K. C., aged 16, a brother of Case No. 5, collapsed and died while riding his bicycle. No previous medical history was available. Post mortem he was found to be a well nourished and well developed young boy whose heart was virtually identical in appearance with that of his sister, showing a localized hypertrophy affecting the anterior wall and interventricular septum. By coincidence on the day of his death his younger sister attended the outpatient department of Hammersmith hospital and was found to have signs identical with her sister. This family will be the subject of another paper.

Dr. J. F. Goodwin, Mr. Donald Ross, Dr. J. Richardson, Dr. E. W. Paul, and Dr. E. D. Acheson have all allowed me the use of clinical notes and electrocardiograms. Dr. Aubrey Leatham has interpreted the latter for me. Miss J. Underhill and Miss S. Fry have photographed the specimens and Professor Crawford has provided the photomicrographs. To all these I am most grateful for help, advice, and encouragement.

References

Adams, R. D., Denny-Brown, D., and Pearson, C. M. (1953). *Diseases of Muscle*. Cassell, London.
Batchelor, T. M., and Maun, M. E. (1945). *Arch. Path.*, **39**, 67.
Browne, G., and Gray, G. (1930). *Lancet*, **1**, 915.
Eulinger, E. (1925). *Virch Arch.*, 257, 719.
Friedberg, C. K. (1949). *Diseases of the Heart*. Philadelphia and London, 1003.
Hueper, W. C. (1955). *Arch. Path.*, **19**, 372.
—— (1941). *Amer. J. Path.*, **17**, 121.
Mahaim, I. (1945). *Les Tumeurs et les Polypes du Cœur*. Paris, Masson.
Saphir, O. (1953). In S. E. Gould's *Pathology of the Heart*. Charles C. Thomas, Illinois.

CARDIAC SYNCOPE IN ATRIAL SEPTAL DEFECT

BY

CORNELIO PAPP

From the Cardiac Department of the London Chest Hospital

Received March 1, 1957

Atrial septal defect (A.S.D.) in adults is often asymptomatic and may be a chance discovery on clinical examination or at mass radiography. Symptoms arise late in the course of the disease and are those commonly seen in other cardiac conditions with right heart failure. Cardiac syncope has not been described as a leading symptom of A.S.D. and must be regarded as a rarity. It may be accidental that within six months of each other two patients came under observation on account of syncope and both had A.S.D. One knew of a cardiac murmur he had since childhood; the other was unaware of any heart disease.

At a time when surgical repair is becoming a routine procedure in A.S.D., any new symptom has an added interest. This and the different mechanism of syncope in the two cases, caused by coexistent arrhythmia in both, justifies this report.

CASE 1. A man, aged 22, a fitter, had known of his cardiac murmur since childhood and was rejected on account of it from military service when aged 18. He never complained of any shortness of breath, and had been able to run for short distances and climb stairs. His effort tolerance thus has been good if not normal.

In May 1955 he cycled hurriedly to work because he was late. He wanted to make an excuse for his late arrival when he suddenly lost consciousness. The first thing he remembered was lying on the couch in the first-aid room some time later; he did not appear to have had a fit, was not incontinent, and did not injure himself. He went back to work and felt perfectly well. One week later he had a sudden attack of giddiness and fell forward on his outstretched hands, injuring himself; he did not lose consciousness but it took him about ten minutes to recover fully. During the next fortnight he had three similar episodes; during the last one he again lost consciousness and became fully conscious only two hours later at the Casualty Department of a nearby hospital.

From May up to his admission to Charing Cross Hospital in October, 1955, he felt perfectly well.

On examination he was a well-built man with no cyanosis or clubbing. The pulse varied from 80 to 90; at times it was regular, at others there were irregularities suggesting extrasystoles. The blood pressure was 120/85.

Clinical examination of the heart showed a right ventricular type of diffuse and tapping cardiac impulse at its normal location. The main finding was a systolic thrill over the pulmonary area; corresponding to this there was a grade III systolic murmur widely heard over the præcordium but loudest over the pulmonary area. The pulmonary second sound was of normal intensity; it was split with delay of the pulmonary component. There were no signs of congestive heart failure; the rest of the examination was normal.

Radioscopy and chest film showed a bulky heart without obvious enlargement; the apex was rounded, the right ventricular conus full, and the main pulmonary artery slightly prominent. In the left oblique position the right ventricle had an increased convexity and the aortic window was obscured by the enlarged left pulmonary branch. The pulmonary vascularity was above average; the pulmonary stem showed increased pulsation but there was no hilar dance; the aorta was small. The cardiogram showed partial right bundle-branch block (Fig. 1.) The diagnosis was that of A.S.D.

After his discharge he took ephedrine gr. ½ twice a day. From November, 1955 to July, 1956 when

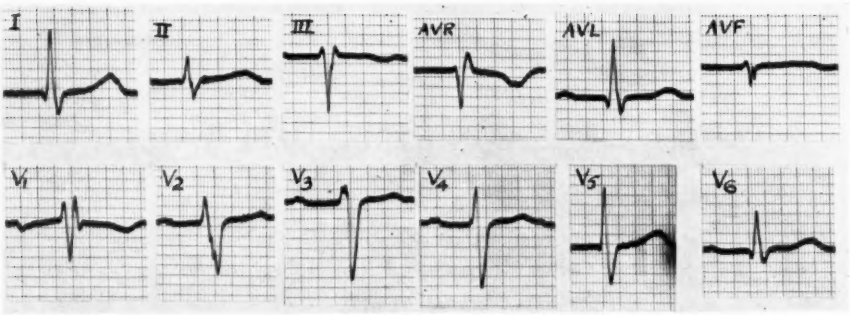


FIG. 1.—Case 1. " M " complex in V1 the only sign of right ventricular hypertrophy; P–R interval=0·26 sec.

he was admitted to the London Chest Hospital he had only two attacks, the latter on June 12. These were shorter and less severe than those in May, 1955. Though they came suddenly he had a short warning; he felt giddy and had a sickly taste in his mouth. He fell to the ground, not completely unconscious, but unable to move.

The clinical, radiological, and electrocardiographic findings were unchanged. Cardiac catheterization confirmed the clinical diagnosis of A.S.D. with a left-to-right shunt of 7·2 l./min. (see Table I). No spontaneous syncopal attacks were observed during the stay in hospital, nor could these be provoked by effort, vagal compression, Valsalva manœuvre, or atropine.

TABLE I

MAIN CARDIAC CATHETER DATA

Case	Pressure: mm. of Hg				Oxygen saturation (%)				A-V O_2 diff. Vol. (%)	Pulm. flow (l./min.)	Syst. flow (l./min.)	L–R shunt (l./min.)
	Right ventricle		Pulmonary artery									
	S/D	Mean	S/D	Mean	SVC	RA	PA	BA				
1	26/2	10	16/5	9	73	84	84	93	4·2	13·0	5·8	7·2
2	28/2	11	28/7	15	62	79	79	91	6·0	8·4	3·5	4·9

The Arrhythmia. The cardiograms recorded during the first hospital admission in October 1955, while he was free from syncopal attacks for four-and-a-half months, were all similar. They consisted of periods containing 3–4 P waves and 4–5 R waves; three of these periods are shown in Fig. 2 ; the lead recorded is V1, where the P waves were normally inverted. The periods start with a QRS complex which is not preceded by a P wave and is therefore a nodal beat (R1, R5, R10); this is followed after a varying interval of 0·32–0·37 sec. by a P wave of normal appearance which rides around the peak of the T wave (P1, P4, P8); the next ventricular complex follows after a fixed distance of 0·34–0·32 sec. (R2, R6, R11). The P–R distance then gradually shortens from 0·24 to 0·18 and to 0·16 and 0·14 and a nodal escape introduces the next period. The P waves follow each other at irregular intervals; after every third or fourth P wave a longer pause follows which in this record is fairly constant (1·28, 1·28, 1·28, and 1·22 sec.) without being a multiple of the previous P–P intervals. Thus there is no sinu-atrial block in the strict sense, but a sinus arrhythmia with periodical sinus standstill. The R–R distances on the other hand are fairly equal with the exception of the one which follows the nodal escape; the average ventricular rate at 80 a minute is faster than the atrial rate at 62 a minute. This suggests atrio-ventricular dissociation. Ventricular captures occur after every nodal escape and this explains the premature appearance of the

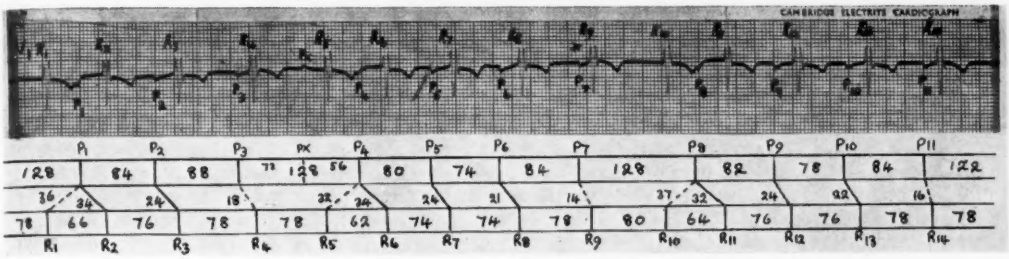


FIG. 2.—Case 1. Electrocardiogram of October, 1955. Lead V1 where P waves were normally inverted. Sinus arrhythmia with sinus standstill, A-V dissociation with interference. Three periods shown consisting of a nodal beat, 1–2 conducted beats, and a dissociated beat. PX=blocked atrial extrasystole separating the first and second period. Full lines=transmitted impulses; interrupted lines=no conduction. Distances in 1/100 of a second. For details see text.

second ventricular complex in every cycle (R2, R6, R11). This is not a reciprocating beat for the P wave has a normal shape which excludes retrograde conduction; furthermore the R–P distance of the nodal escape is variable (0·36, 0·32 and 0·37 sec.) and thus contrasts with the fixed P–R distance of the conducted beat (0·34, 0·34, 0·32 sec.); finally, if atrioventricular dissociation exists there must be uni-directional block which prevents the retrograde spread of the nodal impulse to the atrium. Therefore the upright P wave which appears half-way between the first and second cycle (PX) and does not interfere with the atrial standstill of the basic rhythm (1·28 sec.) is a blocked atrial extrasystole. P2, P5, P6, P9, P10

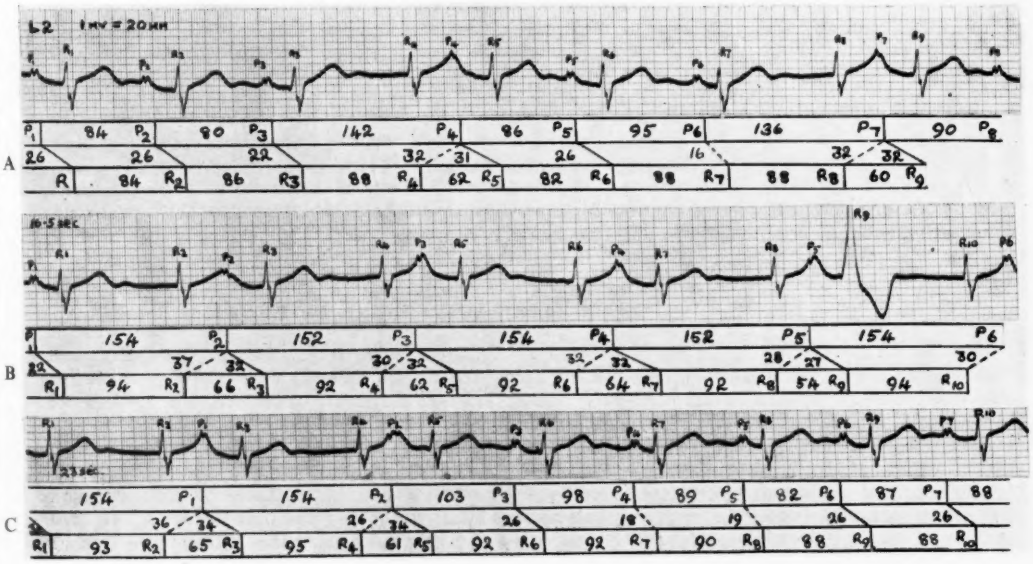


FIG. 3.—Case 1. Electrocardiogram of July, 1956. LII with double standardization shows identical pattern of P throughout. (A) End of effort test. First three cycles show sinus rhythm with P–R=0·26 sec., followed by period formation as in Fig. 3. (B) 16·5 sec. after the end of (A). Sinus bradycardia, atrial rate 39, average ventricular rate of nodal and conducted beats 80. Coupled rhythm formed by nodal and conducted beats persists for 26·5 sec. during maximal deceleration. (C) 23 sec. after the end of (B). At R5 coupling ceases, alternating sinus rhythm with A-V dissociation for 3 beats, then sinus rhythm as in (A).

are also conducted to the ventricle for R3, R7, R8, R12, and R13 are slightly premature when compared with R4, R5, R9, R10, R14 which appear at the genuine nodal distances of 0·78–0·80 sec., representing an inherent nodal rate of 76 a minute. The diagnosis is therefore that of sinus arrhythmia with sinus bradycardia, and atrioventricular dissociation with interference. However, the reason for the syncopal attacks and the prolonged P–R interval of the conducted beats remained obscure until, during an effort test in July, 1956 (when he was admitted for cardiac catheter studies), regular sinus rhythm appeared.

Fig. 3 is from a long strip recorded during an effort test; it shows lead II with double standardization (1m. volt=20 mm.) to enlarge the P waves. The first two beats in (A) are sinus beats with a P–R interval of 0·26 sec.; this was the constant A-V conduction time during the effort test and no faster conduction was seen at a rate of 90 a minute. Thus during sinus rhythm latent heart block is present. As soon as the rate slows, period formation starts again as in Fig. 2, with the usual sequence of nodal escape, two conducted beats, A-V dissociation, and sinus standstill. (B) is part of the same record 16·5 seconds after the end of (A); suddenly the atrial rate diminishes to 39 a minute. Were it not for the nodal escapes the ventricular rate would be just as slow but the nodal escapes added to the conducted beats keep the ventricles at an average rate of 80, double the atrial rate. This rhythm persists for 26·5 seconds. R9 shows aberrant interventricular conduction due to its early appearance in diastole. The magnification of the P waves with double standardization clearly proves that all are of sinus and not of nodal (e.g. retrograde) origin, since their shape remains always the same. At the end of strip (C) recorded 23 seconds after the end of (B) sinus rhythm, with the usual P–R interval of 0·26 sec., reappears.

Further electrocardiograms after effort were recorded five months later in November, 1956, when he felt well and had been without cardiac syncope for six months. The records still showed the period formation as seen in Fig. 2, but the periods were longer, contained more conducted beats, and auricular standstill was shorter and variable. During maximal deceleration the atrial rate averaged 60 and the ventricular rate 85 a minute.

Cardiac syncope in this patient was due to periodical sinus bradycardia which still could be produced 18 months after the first syncopal attack by effort, at a time when the nodal automatism, " the ectopic rhythm by default " was fully effective. It has to be remembered that he had the first faint after an unusual effort, though subsequently he had them at rest as well. Whether prolonged sinus standstill occurred during these attacks or not is open to speculation. Though retrograde conduction from the nodal beat to the sinus was excluded by the normal P wave the reactivation of the sinus 0·30–0·40 sec. after the nodal beat suggests that the latter may have been instrumental in this. The ventricular contraction caused by the nodal impulse may have acted as a mechanical stimulus to the flagging sinus which then continued to function for some beats. Since the length of diastole preceding the nodal beat was almost constant in the single records, it can be presumed that the nodal pacemaker was active all the time, though it was submerged during sinus activity (Lewis, 1925). It is thus conceivable that before nodal automatism was fully developed periods of sinus standstill were responsible for the syncopal attacks, which were then followed by sinus bradycardia and thus produced a state of prolonged semi-consciousness.

CASE 2. A man, aged 58, a painter-decorator, was admitted as an emergency to the Charing Cross Hospital in April, 1956. While washing a wall he became giddy, lost consciousness, fell to the ground, and injured his head. The next thing he remembered was lying on the pavement; he regained consciousness fully about half an hour later in the Casualty Department. On admission he looked pale and was sweating profusely; he had an irregular pulse of 120–140 and a systolic blood pressure of 100. The provisional diagnosis was that of a silent cardiac infarction.

There had been no significant previous illnesses. He had been active always, though he had noticed some shortness of breath during the past year.

He improved quickly and when transferred to the ward a few hours later the blood pressure rose to 140/95; the pulse rate was 110, irregular. There was a loud systolic murmur over the lower end of the sternum, a widely split pulmonary second sound, and a short diastolic murmur. There were no signs of congestive heart failure. A chest film showed moderate cardiac enlargement involving the right ventricle and atrium, and enlargement of the pulmonary artery, with overfilling of the pulmonary branches which showed hilar dance on screening. The aorta was small. The cardiogram (Fig. 4) showed 2:1 flutter with right bundle-branch block; there were no signs of cardiac infarction. The diagnosis was atrial septal defect.

Digitalis in high dosage did not restore sinus rhythm nor did it transform the flutter into fibrillation. He was discharged after six weeks, with a 3:1 flutter (A.R.210–V.R.70).

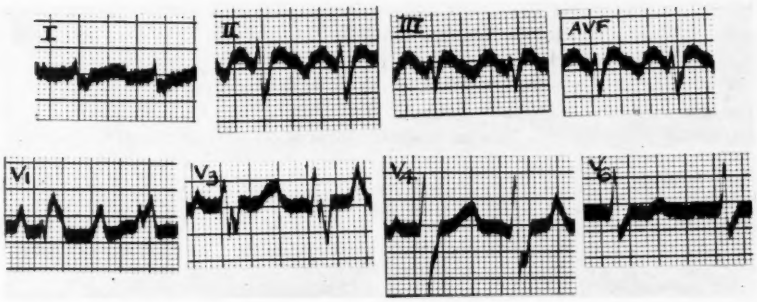


FIG. 4.—Case 2. Electrocardiogram of April, 1956, two days after syncope, showing 2:1 auricular flutter, right bundle-branch block, and right ventricular hypertrophy.

Cardiac catheter studies at the London Chest Hospital three months later confirmed the clinical diagnosis; there was a left-to-right shunt of 5 l./min. with normal pressures in the right chambers and pulmonary artery (see Table I). Attempts to restore normal rhythm were again unsuccessful and he was discharged with a 4:1 flutter (A.R.232–V.R.58).

When seen in November, 1956, as an outpatient he felt well and had been working in a lighter occupation. There had been no further syncopal attacks, and the 3:1 flutter was kept in control with digitalis.

The syncopal attack in this patient was produced by sudden change of rhythm; the low cardiac output during 1:1 or 2:1 flutter caused the shock-like state present on admission.

DISCUSSION

The cause of syncope in both cases was the same, the arrhythmia associated with A.S.D., but the mechanism was different. In Case 1 it was due to impulse inhibition as shown by non-phasic sinus standstill; in Case 2 it was due to rapid impulse formation possibly to 1:1 flutter. Since all forms of arrhythmia in A.S.D. are thought to be common (Taussig, 1947) one wonders why syncope is so exceptional. The incidence of arrhythmias in A.S.D. varies in the published series; in the older ones before cardiac catheterization became a common diagnostic procedure they were considered to be frequent. Out of 10 patients coming to necropsy (Bedford *et. al.*, 1941) four had auricular fibrillation and in all these there was associated mitral stenosis. Out of 43 clinical cases only two had auricular fibrillation and one of these had mitral stenosis. In a recent series of A.S.D. comprising 95 cases by Walker *et. al.* (1956), all proved by cardiac catheter, and of ages ranging from 5 to 40 years, arrhythmias were exceptional and consisted of a few extrasystoles in one and alternating sinus and nodal rhythm in another.

Cardiac arrhythmias in A.S.D. may arise under two different circumstances. Commonly they arise when the disease is progressing, when the atria dilate, and when other predisposing factors such as advancing age and mitral stenosis co-exist. These were the arrhythmias of the older series where the diagnosis was either made at post-mortem examination or when the disease was advanced. The type of arrhythmia was that found in any heart disease, whether congenital or acquired, that involves the atria, i.e. auricular fibrillation or flutter. Case 2, aged 58, is an example.

Rarely auricular arrhythmias are associated with A.S.D. in young people where there is little or no cardiac enlargement, and the cardiogram shows slight right ventricular hypertrophy or only the partial right bundle-branch block. The arrhythmia here is of a complex pattern as in Case 1, or may be of the type of partial heart block (Campbell and Thorne, 1956). These are examples of genuine congenital arrhythmias. Whether they are coincidental with or caused by A.S.D. cannot be decided though the frequent presence of latent heart block in A.S.D. suggests a causal relationship.

Surgical correction was not indicated in either of these patients. The defect was small and the

shunt amounted to only 30 per cent more than the systemic blood flow. Case 1, a young adult, had no cardiac enlargement and the cardiogram with an M complex in V1 suggested only a slight degree of right ventricular hypertrophy. Case 2, aged 58, had some cardiac enlargement and signs of incipient heart failure which were easily corrected by digitalis; in view of his age and the persistent flutter, operation was considered too risky. Moreover, the symptoms in both patients were not due to A.S.D. but to the co-existent arrhythmia. The physiological compensatory mechanism of nodal automatism worked satisfactorily in Case 1 and he has not had syncopal attacks for eight months; in Case 2, still in flutter, digitalis maintains a 3:1 block and assures a slow ventricular rate.

Summary

Cardiac syncope was the only symptom in two cases of atrial septal defect, both with a small shunt. It was caused in the first patient, aged 22, by impulse inhibition through non-phasic atrial standstill, thought to be due to congenital arrhythmia. Compensatory nodal automatism, giving rise to A-V dissociation abolished the attacks. In the second patient, aged 58, syncope was caused by rapid impulse formation through sudden onset of flutter; the arrhythmia here was related to the evolution of the disease and syncope was abolished by reduction of the ventricular rate.

I am greatly indebted to Dr. K. Shirley Smith, Physician to the Cardiac Department for permission to publish these cases under his care. I also wish to thank Dr. Elizabeth A. Priest and Dr. Ronald Gibson for the cardiac catheter data.

References

Bedford, D. E., Papp, C., and Parkinson, J. (1941). *Brit. Heart J.*, **3**, 37.
Campbell, M., and Thorne, M. G. (1956). *Brit. Heart J.*, **18**, 90.
Lewis, Sir Thomas (1925). *The Mechanism and Graphic Registration of the Heart Beat.* 3rd ed., Shaw & Sons, London.
Taussig, H. B. (1947). *Congenital Malformations of the Heart.* Commonwealth Fund, New York.
Walker, W. J., Mattingly, T. W., Pollock, B. E., Carmichael, D. B., Inmon, T. W., and Forrester, R. H. (1956). *Amer. Heart J.*, **52**, 547.

FIBRINOLYSIS IN MYOCARDIAL INFARCTION

BY

ROBERT HUME

From The University Department of Medicine, Royal Infirmary, Glasgow

Received March 29, 1957

Fibrinolysis is the process of fibrin digestion by an enzyme system present in the blood. Although fibrinolytic activity has been found in the normal, and in many pathological states, its rôle remains obscure. It seems likely, however, that such a process may take part in the normal hæmostatic equilibrium of the body and may be operative in the processes of resolution and healing (Astrup, 1956).

This paper records serial observations with respect to this fibrinolytic activity in cases of myocardial infarction.

Materials and Methods

Preparation of reagents. 3·8 per cent sodium citrate and M/40 calcium chloride were prepared as described by Biggs and Macfarlane (1953).

Thrombin was prepared by the method of Biggs and Macfarlane (1953) from plasma obtained from expired bank blood. The thrombin was divided into 2 ml. lots and stored at −20° C. Fresh samples were used each day and diluted with normal saline so that the clotting time of 0·2 ml. plasma and 0·2 ml. thrombin was 15 seconds.

Buffer. To 5·0 ml. of stock solution of sodium acetate/sodium veronal (9·714 g. of Na.OAc $3H_2O$ and 14·714 g. Na. veronal made up to 500 ml. in CO_2 free water) was added 5·0 ml. of 0·1 per cent hydrochloric acid and 15 ml. distilled water (*p*H 7·4 measured by *p*H meter). Fresh buffer was made on alternate days from stock solution.

Glassware. ½ × 3-inch tubes were used throughout. The tubes were washed with a solution of deosan detergent, thoroughly rinsed and dried overnight in an oven at 100° C.

Collection of specimens. Blood was collected by clean venepuncture through a wide-bore needle (S.W.G. 18), care being taken to avoid frothing; 9 ml. of blood was delivered into an ice-cold 10 ml. graduated centrifuge tube containing 1 ml. of sodium citrate. The centrifuge tubes were surrounded with ice in a glass container for transport to the laboratory. The specimens were collected between 9 and 10 a.m. and centrifuged at 4° C. for 3–5 minutes at 6000 r.p.m. in a refrigerated centrifuge using a high-speed attachment. The interval between collecting the blood and starting the estimation of the fibrinolytic activity varied between ½–1 hour.

Measurement of fibrinolytic activity. A modified dilution technique was employed (Macfarlane and Biggs, 1946). Two sets of five tubes were prepared as follows: ½ ml. of normal saline was added to each tube in a water bath at 37° C.: ½ ml. of plasma was added to the first tube and doubling dilutions made, giving dilutions of 1 : 2, 1 : 4, 1 : 8, 1 : 16, 1 : 32. The 1 : 2 dilution was not used in the test. One row of tubes was immediately clotted by the addition of ½ ml. of thrombin solution to each tube and the other row was clotted by the addition of ½ ml. of calcium chloride solution to each tube. The lysis time was estimated from the addition of calcium and thrombin. One hour after the addition of thrombin and calcium ½ ml. of buffer was added to each tube. The tubes were gently agitated in order to free the clot from the sides. The total amount in each tube was

1·5 ml. Fearnley and Lackner (1955) have shown that fibrinolysin is not diluted by the addition of buffer after clotting has occurred.

Readings. The tubes were inspected at 6 hours and 24 hours. The number of tubes in which complete lysis had occurred, that is in which the clot had completely disappeared or disintegrated, was counted. The number of tubes lysed at 6 hours was added to the number found lysed at 24 hours. As there were two rows of four tubes the highest possible number lysed on any one inspection was eight. The maximum activity recordable by this means was therefore sixteen. It was hoped in this way to make more apparent the difference between rapid lysis and lysis that took 24 hours to complete.

Patients. Ten patients (seven men and three women) diagnosed clinically and confirmed by electrocardiography as having myocardial infarction (nine showing well-marked Q wave changes and the tenth irrefutable sequential changes) were examined daily for fibrinolytic activity for

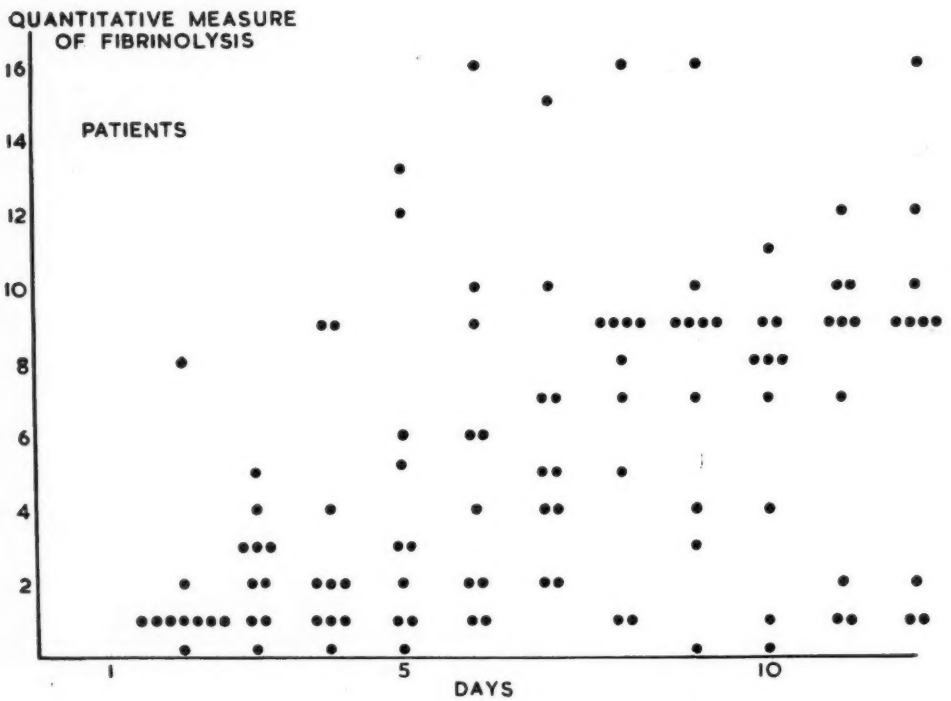


FIG. 1.—The individual daily readings of the ten patients with myocardial infarction are plotted for the first twelve days.

twenty-eight days. The first estimation was made on the day following the episode. On admission each patient received a single injection of 40,000 I.U. of heparin in a modified Pitkin's menstruum (Boots) intramuscularly and 200 mg. of phenylindanedione orally. The phenylindanedione was continued throughout the period of observation, the dose being regulated by daily estimations of the one-stage clotting time.

Controls. Ten patients (five men and five women) who had been admitted to the mental observation wards in the Eastern District Hospital, Glasgow, were used as controls, and followed for a similar period.

Effect of heparin. Observations were made on three of the controls who were given a single injection of 40,000 I.U. of heparin in a modified Pitkin's menstruum intramuscularly.

Effect of phenylindanedione. One patient who was admitted with severe chest pain and subsequently showed no evidence of myocardial infarction was given phenylindanedione alone, by mouth over a period of eight days, and observations made.

Effect of shock. Ten patients admitted to the surgical wards as acute emergencies were examined for fibrinolytic activity the day following admission. These patients were suffering from a variety of conditions varying from fractured limbs and crush injuries to abdominal emergencies.

RESULTS

The individual results for the first twelve days of the ten patients with myocardial infarction are plotted in Fig. 1. The individual results of the ten controls for the first twelve days are plotted in Fig. 2. The mean daily readings are shown graphically for the twenty-eight days in Fig. 3, in

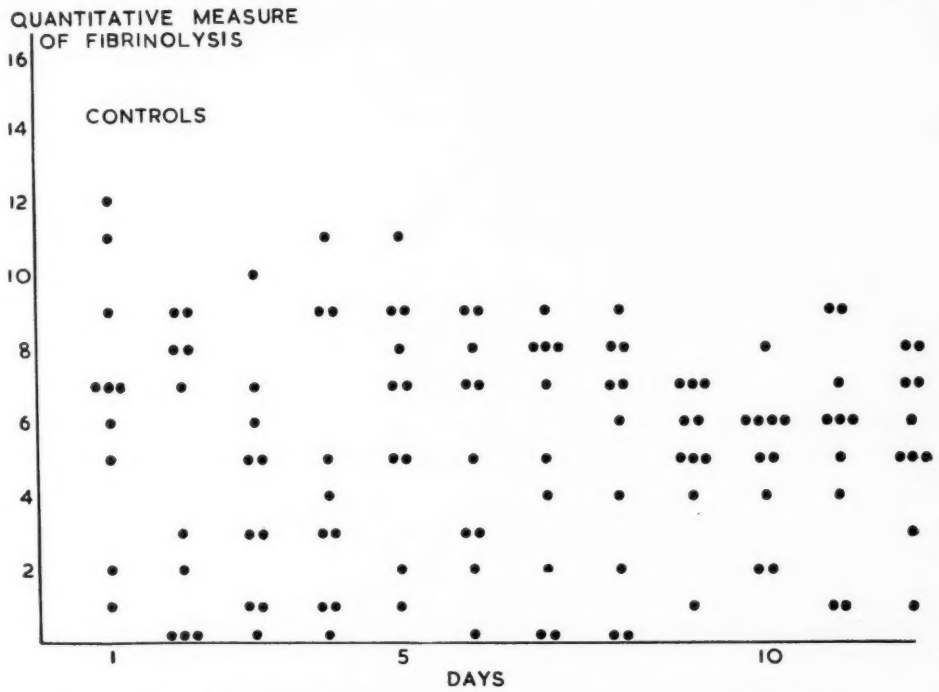


FIG. 2.—The individual daily readings of the ten controls are plotted for the first twelve days.

which those of the patients are contrasted with those of the controls. Analysis of variance showed that for the ten controls there was no significant day-to-day variation ($F=1{\cdot}03$, $P>0{\cdot}05$). The patients with myocardial infarction showed, however, a significant day-to-day variation ($F=3{\cdot}49$, $P<0{\cdot}01$). The day-to-day variation from the ninth to the twenty-eighth day after the episode was considered and no significant variation was found ($F=1{\cdot}36$, $P>0{\cdot}05$) but the second to the eighth days showed a significant day-to-day variation ($F=6{\cdot}60$, $P<0{\cdot}01$). Fig. 3 shows that the fibrinolytic activity increases uniformly with time over the first eight days. It would appear, therefore, that following myocardial infarction there was a depression of fibrinolytic activity which only reverted to normal levels after eight days.

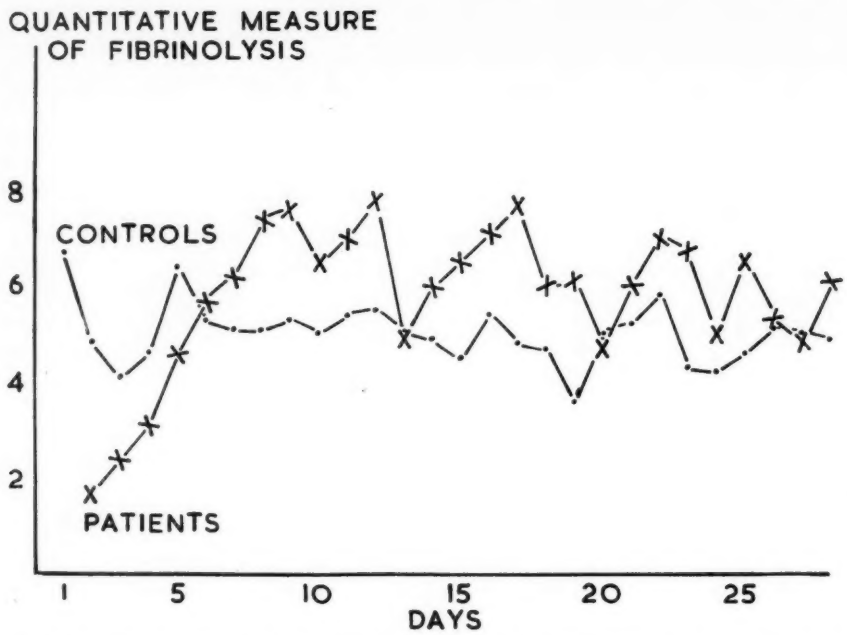


FIG. 3.—The mean daily readings of the ten patients with myocardial infarction and the ten controls are contrasted. The fibrinolytic activity of the patients with infarction increases uniformly with time over the first eight days. There is no statistically-significant day-to-day variation in the controls.

It seemed important, however, to eliminate three possibilities as having given rise to this phenomenon. First, was the initial injection of heparin responsible for the depression of fibrinolytic activity? Heparin has been reported to inhibit fibrinolysis in *in vitro* study (Astrup and Alkjaersig, 1952) and it has been suggested that it potentiates its action if given intravenously (Greig, 1956). Three of the controls were therefore given 40,000 I.U. of heparin in a modified Pitkin's menstruum intramuscularly and observed over the next fourteen days. The results were unlike those produced by the coronary patients and were compatible with normal fluctuation in activity.

It did not seem likely that the phenylindanedione was responsible as this drug had been continued throughout the period of observation after normal levels of fibrinolytic activity had been obtained. However, one patient who was admitted with severe chest pain and subsequently showed no evidence of myocardial infarction was given phenylindanedione alone by mouth, and observed over eight days. There was no depression in fibrinolytic activity and the result was of interest, too, in that it was in keeping with the negative laboratory findings of myocardial infarction.

The third possibility that was examined was whether the reaction was a non-specific one to some severe physically disturbing incident. The mean of the results made on the ten surgical patients is shown by histogram in Fig. 4 labelled " surgical." This is compared on the same diagram with the mean reading of the first day results made on the coronary patients, with the mean daily reading of the controls and with the mean reading of eighty sporadic observations made on eighty different patients, excluding patients with myocardial infarction and liver disease. The scatter of results is similar to that of the controls and the mean reading is not significantly different although significantly different from the coronary patients. It would appear, therefore, that the reaction is not a non-specific one to " shock," the word shock being used in its broadest sense as the patients with myocardial infarction were in fact not all clinically shocked.

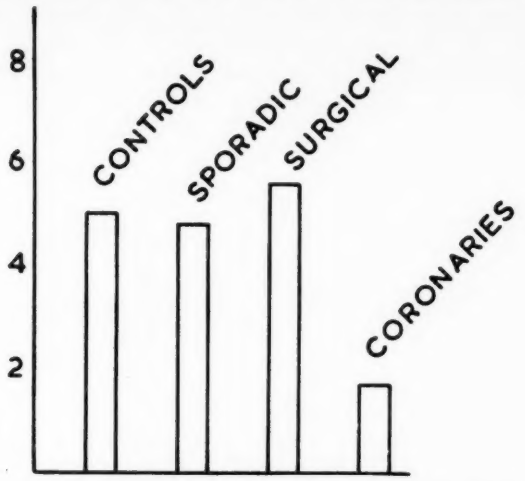


FIG. 4.—Quantitative measure of fibrinolysis. The mean reading of the ten "shocked" patients labelled "surgical" is compared with the mean reading of the first-day results made on the patients with myocardial infarction, with the mean daily reading of the controls and with the mean reading of eighty sporadic observations made on eighty different patients.

DISCUSSION

The ætiology of myocardial infarction is uncertain. It is not known whether the cause lies in the wall of the coronary artery or in the contained blood. Duguid (1954, 1955) has presented evidence to show that mural thrombi may form and lead to atheromatous plaque formation. Others have claimed that following myocardial infarction there may be an alteration in blood coagulation (Hines and Kessler, 1945; Ogura *et al.*, 1946; Peel, 1953, 1956). Fibrin formation in the coronary vessel is, therefore, of importance in this condition whether in the ætiology of atheroma or in the formation of the thrombus.

In the formation of fibrin, there is a balance of activators and inhibitors. Similarly in the removal of fibrin by fibrinolysis there is probably a balance of activators and inhibitors. As distinct from the system leading to the formation of fibrin, the system capable of removing fibrin may be of equal importance in this condition.

The systems for the formation and the removal of fibrin may be intimately related, as it has been shown that dietary fats can accelerate coagulation *in vitro* (MacLagan and Billimoria, 1956; O'Brien, 1956; Barkham *et al.*, 1956) and possibly inhibit fibrinolysis (Greig, 1956).

It is not possible, at present, to put a final interpretation on the phenomenon described. It does not appear likely from the evidence presented that the depression of fibrinolytic activity following myocardial infarction was due either to the initial injection of heparin or to phenylindanedione, nor was it a non-specific reaction to some severe physically disturbing incident as evinced by the observations on the surgical patients. It could possibly, however, represent a change in the blood that has favoured the occurrence of myocardial infarction, but the fact that the changes generally last for eight days would then be unlikely.

SUMMARY

This paper reports the results of measurement of fibrinolytic activity in patients following myocardial infarction. The fibrinolytic activity was studied in ten patients for twenty-eight days subsequent to the episode and compared with ten controls. In the patients with myocardial

infarction there was depression of fibrinolytic activity and this did not reach normal levels until after eight days. It did not appear that the treatment received by the patients was responsible for this phenomenon, nor was it a non-specific reaction to some severe physically disturbing incident.

I wish to thank Professor L. J. Davis for his helpful advice and criticism in the preparation of this paper and also Professor W. A. Mackey, Mr. C. J. Longland, and Dr. I. M. Sclare for permission to investigate their patients. I am also grateful to Dr. R. A. Robb for the statistical analysis of the results, to Dr. A. S. Douglas for his interest in this work, and to the Advisory Committee on Medical Research for Scotland for defraying part of the cost of the equipment. Most of this work was done during the tenure of the Hutchison Research Scholarship.

REFERENCES

Astrup, T., and Alkjaersig, N. (1952). *Nature, London*, **169**, 314.
—— (1956). *Blood*, **11**, 781.
Barkham, P., Newlands, M. J., and Wild, F. (1956). *Lancet*, **2**, 234.
Biggs, R., and Macfarlane, R. G. (1953). *Human Blood Coagulation and Its Disorders*. Blackwell, Scientific Publications. Oxford.
Duguid, J. B. (1954). *Lancet*, **1**, 891.
—— (1955). *Brit. med. Bull.*, **2**, 36.
Fearnley, G. R., and Lackner, R. (1955). *Brit. J. Hæmat.*, **1**, 189.
Greig, H. B. W. (1956). *Lancet*, **2**, 16.
Hines, L. E., and Kessler, D. L. (1945). *Arch. intern. Med.*, **75**, 248.
Macfarlane, R. G., and Biggs, R. (1946). *Lancet*, **2**, 862.
MacLagan, H. F., and Billimoria, J. D. (1956). *Lancet*, **5**, 235.
O'Brien, J. R. (1956). *Lancet*, **5**, 432.
Ogura, J. H., Fetter, N. R., Blankenhorn, M. A., and Glueck, H. I. (1946). *J. clin. Invest.*, **25**, 586.
Peel, A. A. F. (1953). *Brit. Heart J.*, **15**, 8.
—— (1956). *Brit. Heart J.*, **18**, 378.

THE EFFECTS OF ACUTE CARDIAC INFARCTION AND OF HEPARIN THERAPY ON THE LIPOPROTEINS

BY

E. M. M. BESTERMAN

From the Institute of Cardiology

Received May 27, 1957

In a comparison of the lipoprotein patterns found in the sera of ischæmic and control subjects, an increased pre-β lipoprotein (Dangerfield and Smith, 1955), was found in 99 per cent of 200 patients with ischæmic heart disease (Besterman, 1957). Further analysis of these findings showed that the pre-β lipoprotein was most plentiful in those with acute coronary insufficiency and least in those seen within a few hours of acute cardiac infarction. As many of these patients received anti-coagulant therapy the effects of heparin on the lipoprotein patterns have also been investigated.

The serum lipoproteins were studied by paper electrophoresis as previously described. The proportion of each of the three lipoproteins, β, pre-β, and α, was determined by planimetry of graphs derived from the paper electrophoretograms. As no strict quantitative accuracy can be expected from paper electrophoresis, the area of each lipoprotein has been expressed as a fraction of the total area of lipoproteins present.

Acute Infarction. The quantity of pre-β lipid present in the sera of patients with angina of effort was similar to that found in the sera of patients with established cardiac infarction (Table I).

TABLE I

PRE-β LIPOPROTEIN FRACTION IN DIFFERENT TYPES OF ISCHÆMIC DISEASE

	Angina of effort	Acute coronary insufficiency	Acute cardiac infarction	Established cardiac infarction	Controls
Pre-β fraction ..	0·207±0·012	0·235±0·017	0·1±0·029	0·213±0·009	0·008±0·01
Number of patients	60	35	15	105	78

However, patients with a typical history and the electrocardiographic changes of acute coronary insufficiency had a greater amount of pre-β lipid, whereas patients seen within 24 hours of acute cardiac infarction had a significantly diminished pre-β fraction (Fig. 1). This change has also been observed by Smith (1956). Fifteen cases were studied within a day of the onset of infarction: little or no pre-β lipoprotein was present in the sera of seven of these and a reduced pre-β fraction was present in the remaining eight. Similarly this fraction was reduced or absent in 19 patients first studied one to three days after infarction (Table II). Subsequent studies on sera from these cases showed the appearance of a marked pre-β lipoprotein, attaining maximum proportions two to three weeks after the acute episode. The fraction then diminished over succeeding weeks and eventually remained at the level observed in cases of established infarction. No significant difference in the β or α lipoproteins was observed in these patients with acute infarction. Similarly no difference in distribution of β and α fractions was found on comparison of the four groups of ischæmic patients shown in Table I. No cases were studied immediately before infarction,

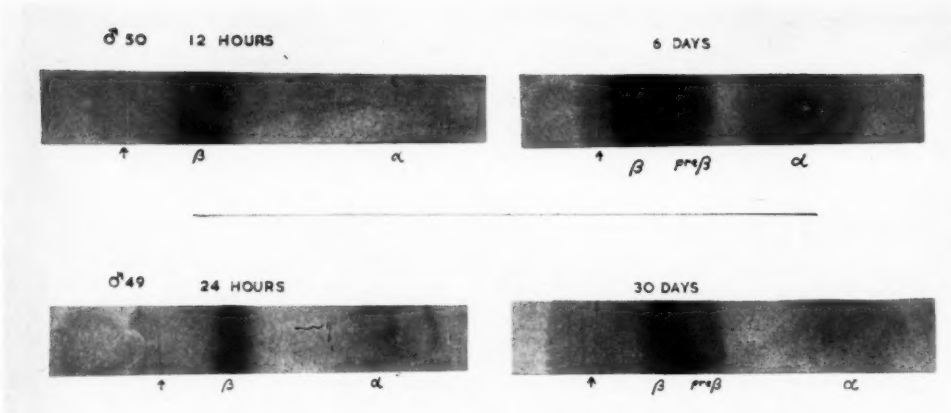


FIG. 1.—Lipoprotein pattern in cardiac infarction; pre-β lipid absent at the acute stage, but present subsequently.

TABLE II

PRE-β FRACTION FOLLOWING ACUTE INFARCTION

Days after infarct	1	1–3	7	14	21	28
Pre-β fraction ..	0·1±0·029	0·169±0·021	0·213±0·018	0·225±0·011	0·237±0·016	0·227±0·013
Number of patients ..	15	19	16	10	11	11

but one patient was seen shortly after each of three acute infarcts and was observed in the intervening periods. Little or no pre-β lipoprotein was present at the time of each infarct; whereas after recovery this lipid was present to a significant extent. Thus it appears that the pre-β lipoprotein alone shows changes during the course of acute cardiac infarction.

EFFECTS OF HEPARIN

Since the original observations by Hahn (1943) that heparin reduced serum turbidity, there have been many reports on the effects of this substance on lipoproteins. Ultracentrifuge studies by Graham *et al.* (1951) showed a redistribution of the Sf groups after heparin: there was a reduction of the larger particles and of the Sf 20–100 fraction with a corresponding increase of the Sf 6–12 groups. Using electrophoresis, Rosenberg (1952) demonstrated increased mobility of both β and α lipoproteins after heparin, without changes in the plasma proteins. Spitzer (1952) found that heparin had no effect on the total fat content of serum, but caused a redistribution of the lipids.

The majority of patients treated for coronary insufficiency or recent infarction received anticoagulant therapy. The opportunity was taken for observing the effects of heparin on the lipoprotein patterns in these cases. Heparin 100 mg. was injected intravenously, blood samples being obtained before injection and at 20 minutes, at one, and at four hours afterwards. Some patients received subsequent heparin injections and in all, the effects of 122 injections in 89 patients were studied. To ensure comparable results, electrophoresis was carried out simultaneously on the four serum specimens from each case. Electrophoresis of the same sera was repeated two or three times in order to verify the findings.

Results. Owing to errors of technique no satisfactory interpretation of results was possible following 21 injections in 10 patients. After the remaining 101 heparin injections, reduction or disappearance of the neutral fat occurred in all cases in which it was initially present. In 10 per cent there was no change in lipoprotein pattern following heparin. However, three different changes were seen in the remaining 90 per cent: increased mobility of both β and α lipid in 30 per cent, increased migration of the β lipid alone in 24 per cent, and disappearance of the pre-β fraction without any alteration of mobility of the β and α lipoproteins in 36 per cent. Increased mobility of the lipoproteins frequently resulted in poor definition of their boundaries and planimetry was therefore only undertaken on graphs obtained from those electrophoretograms in which the lipoproteins were distinctly delineated.

The neutral fats or triglycerides are particles of larger size than the lipoproteins and fail to migrate on paper electrophoresis. They adhere to the paper at the site of application of the serum and, if present in quantity, form a distinct band at this point. However, many patients with recent cardiac infarction had not eaten for some time before admission to hospital, and in these cases little or no neutral fats were found. When present, the triglycerides were invariably reduced by heparin. This action of heparin is analogous to the reduction of visible lipæmia in post-prandial sera by the drug. An absolute diminution of serum neutral fat content following heparin has been shown by Herzstein *et al.* (1954) and Nikkila (1954). This clearing action of heparin has been extensively investigated and it is believed that heparin is not the actual clearing agent, but that it is a necessary precursor of the clearing factor (Anfinsen *et al.*, 1952). After heparin injections Grossman (1955) found that hydrolysis of the triglycerides occurred with an increase of serum fatty acids and it appears that the clearing factor is lipoprotein lipase (Korn, 1955). Grossman (1955) considered that this process might be a normal part of the cycle of fat metabolism in man: this view is supported by the demonstration of endogenous clearing factor (Engelberg, 1955).

In nine patients no change in lipoprotein pattern was seen following eleven heparin injections (Fig. 2). There was no apparent technical fault, and the refractory lipoprotein state appeared to be a true finding. It was of interest that six of these subjects were suffering from acute infarcts. Moreover one was subsequently treated for two further acute infarcts and on each occasion proved to be resistant to the antilipæmic action of the drug (M.C., Fig. 2). Heparin sensitivity tests were not performed and clotting times were not estimated as a routine. The three remaining patients who proved refractory to the antilipæmic effects of heparin had had acute infarcts within the previous two weeks.

Increased mobility of both β and α lipoproteins occurred following 30 heparin injections in 25 patients (Fig. 3). Satisfactory graphs were obtained from 16 of these electrophoretograms. After heparin the β lipoprotein migrated 7 mm. further than before injection, an increase of 11·5 per cent. No distinct pre-β lipid could be seen in any of these electrophoretograms following heparin injection. It was not initially apparent whether the pre-β failed to accelerate and was consequently concealed by the more mobile β fraction, or whether its own mobility had increased to such an extent that it had fused with the α lipoprotein. However, calculations from the graphs suggested that an increase of both β and α fractions had occurred following heparin. If this increase can be ascribed to redistribution of the pre-β lipid alone, 64 per cent of the pre-β fraction was apparently merged with the β and 36 per cent with the α lipoprotein. Hypermobility of the α lipoprotein occasionally resulted in its migration beyond the albumin band of the plasma proteins. In such cases a distinct pre-albumin protein was found as described by Herbst *et al.* (1954). Otherwise the plasma proteins were completely unaffected by heparin.

Increased mobility of the β fraction alone occurred following 28 heparin injections in 20 patients. In these cases the α lipid was unaffected. Analysis of 16 graphs from these electrophoretograms showed an 11 per cent increase of β migration after heparin. The pre-β lipid was no longer detectable and its redistribution following heparin was apparently similar to that found in the previous cases, 67 per cent being added to the β and 33 per cent to the α fractions.

Disappearance of the pre-β lipid occurred in the absence of any increased migration of either

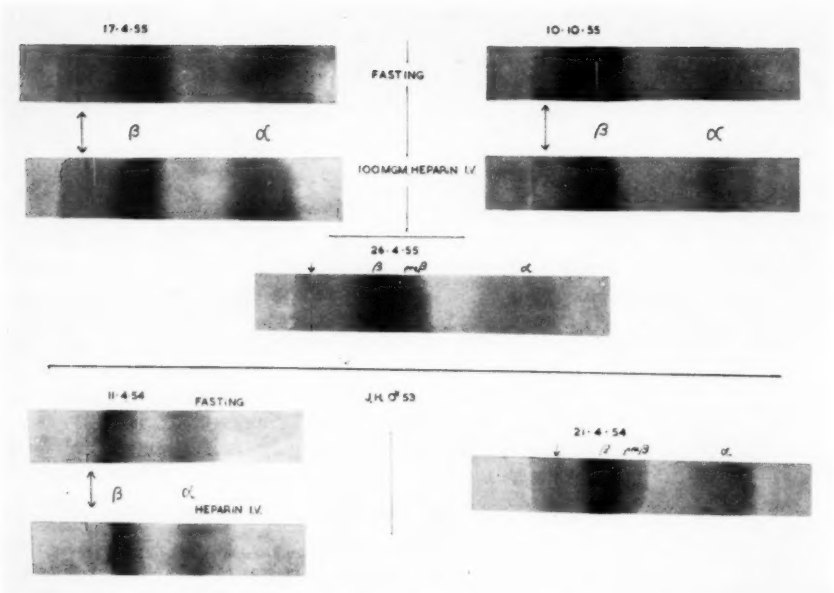


FIG. 2.—Absent pre-β lipid in acute cardiac infarction with no change in lipoproteins following intravenous heparin. Appearance of pre-β subsequently.

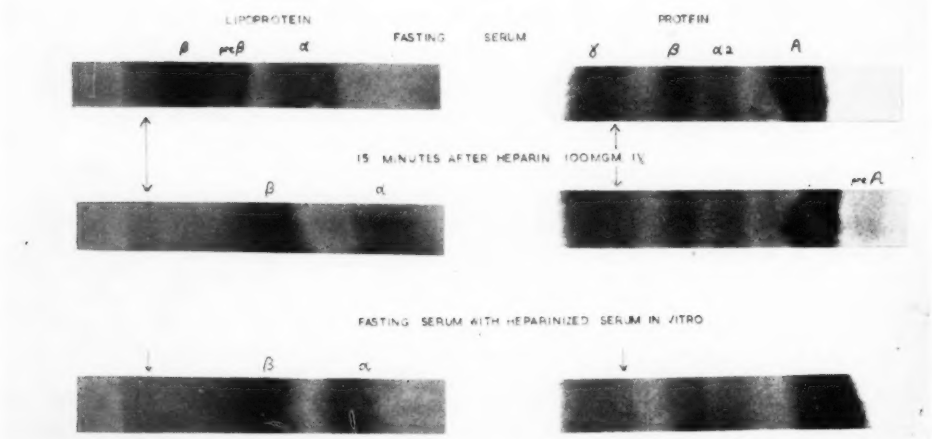


FIG. 3.—Increased mobility of β and α lipoproteins following both intravenous heparin and addition of heparinized serum in vitro.

β or α lipoproteins, after 31 heparin injections in 30 patients (Fig. 4). Graphs derived from 29 of these electrophoretograms were studied. This was of particular interest and has not been reported previously. The apparent redistribution of the pre-β lipid was surprisingly similar to that found in the two previous groups of cases. Of the increase in β and α fractions, 70 per cent occurred in the former and 30 per cent in the latter. No change occurred in the proteins of the sera after heparin.

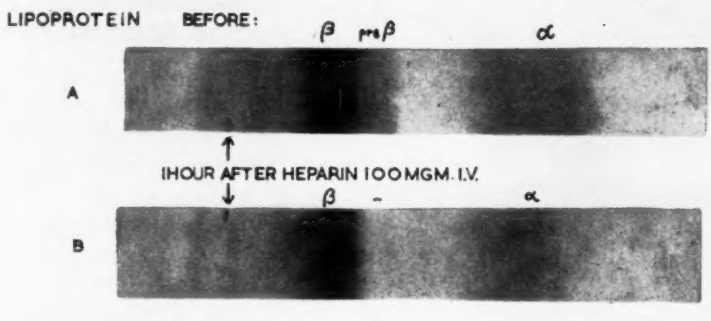


FIG. 4.—Disappearance of pre-β lipid following heparin, without alteration in mobility of β and α lipoproteins.

Thus it appears that of all three lipoproteins the pre-β is most consistently altered following systemic heparin. There was no obvious clinical difference between the patients whose sera showed the varying responses to intravenous heparin. The results of the heparin were always apparent within two minutes of injection and persisted for 18 to 24 hours.

In Vitro Heparin.—The effects of heparin in vitro were then investigated. Anderson (1950) showed that serum obtained from a heparinized subject would clear the turbidity of another serum in vitro. The action of heparinized serum was studied in 14 cases: in all of these increased migration of the β lipoprotein occurred, a 12 per cent increase on comparison with the control serum, and in some the α was also affected (Fig. 3). The pre-β lipoprotein present previously could no longer be discerned after addition of heparinized serum. 80 per cent of the pre-β lipid appeared to become merged with the β and 20 per cent with the α lipoproteins.

Heparin alone in vitro is reputedly without effect. Nevertheless it was decided to study this problem. 100 units of heparin were added to 1 ml. of serum and left at room temperature for one hour. This provided a concentration of heparin 50 times greater than that obtained in vivo with the usual therapeutic dosage. A significant lipoprotein redistribution occurred in 12 out of 14 sera to which heparin was added (Fig. 6). An 18 per cent increase of β lipid mobility was observed following heparin, the α being little altered. The redistribution of the pre-β fraction was again similar to that found after heparin in vivo, 71 per cent being added to the β and 29 per cent to the α fractions.

Thus it appears that both heparinized serum and high concentrations of heparin in vitro can alter the lipoprotein in a manner similar to that found with systemic heparin. In vitro studies with heparin never reproduced the in vivo effect of a reduced pre-β lipid without hypermobility of the β and α fractions.

Heparin in Acute Infarction. A similar reduction of pre-β lipid was thus found both in some cases of acute infarction and in one-third of the cases following intravenous heparin—those without altered mobility of β and α lipids. The effects of heparin were therefore studied in 17 patients treated within 24 hours of infarction. The sera from six of these showed no change after systemic

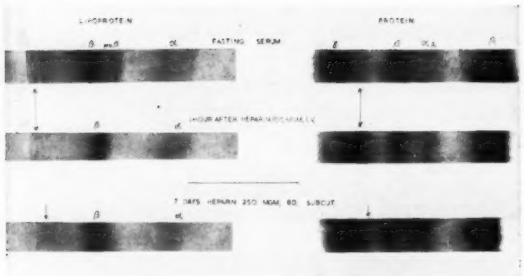


FIG. 5.—Persistent change in lipoprotein pattern produced by daily subcutaneous heparin therapy.

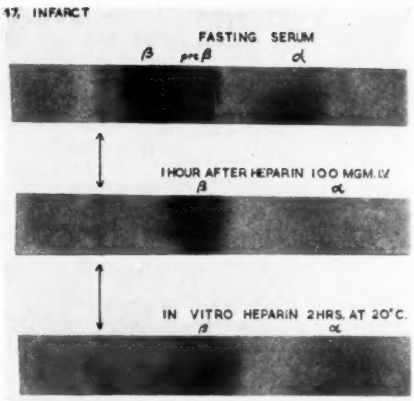


FIG. 6.—Similar effect of intravenous heparin and of in vitro heparin on lipoprotein mobility.

heparin (Fig. 2). One (upper part, Fig. 2) was treated for three acute infarcts during 18 months and was refractory to heparin on each occasion. Thus there were eight episodes of infarction in which heparin had no effect on the lipid pattern: in none of these was any obvious pre-β lipoprotein present at the acute stage, but it subsequently appeared. A pre-β lipid was present in the sera of the remaining 11 patients. After heparin, the pre-β fraction alone was affected in five, and increased mobility of the β and α fractions occurred in six cases.

It has been suggested that heparin or a heparin-like substance is normally secreted by the body. Studying peptone shock in dogs, Havel (1954) and Worley (1955) have demonstrated prolonged clotting times and release of clearing factor. These effects have been ascribed to secretion of endogenous heparin. The mast cells are considered to be a possible source of endogenous heparin and Cairns (1954) has noted an inverse correlation between tissue mast-cell content and susceptibility of the subject to alimentary lipæmia. In human hearts lower mast-cell counts were found in atheromatous than in healthy subjects.

The apparent heparin-resistant state of some patients with acute infarction might be ascribed to a pre-existing heparin effect following endogenous secretion in response to the stimulus of infarction. This is suggested by the absence of a pre-β lipid in these refractory cases, whereas all those showing a response to heparin had a pre-β lipoprotein. Furthermore five of the resistant cases had extensive infarcts and three of them were also suffering from shock. The similarity of lipoprotein pattern in some cases of acute infarction to that found after systemic heparin suggested that prolonged heparin therapy might be of value.

Prolonged Heparin Therapy. Three patients have been treated with daily heparin for three weeks and one for over a year, with adequate lipoprotein studies. In two, with recent infarction, heparin was substituted for dindevan in view of continued ischæmic pain despite complete rest. The third was admitted within two hours of a first infarct. The fourth suffered from hypercholesterolæmia, severe xanthoma tuberosum and tendinosum, as well as ischæmic heart disease; he developed an infarct while under observation in hospital, and heparin was then started. All four received anticoagulant doses, 250 mg. subcutaneously twice daily for three weeks. The fourth patient, with xanthomatosis, thereafter continued single daily injections of 250 mg. of heparin, and this reduced dosage was adequate for an anti-lipæmic action of 24 hours' duration.

No untoward effects occurred. In two cases local pain made it necessary to add 1 ml. 2 per cent procaine to each injection of heparin (250 mg./1 ml.). Subcutaneous administration is less

likely to cause hæmatomata than intramuscular injections. However subsequent experience with further patients has shown that subcutaneous injections in women frequently cause local hæmorrhage.

The lipoprotein pattern was consistently altered in all four cases throughout the period of treatment (Fig. 5). Increased mobility of both β and α lipoproteins persisted, and no pre-β fraction was visible: 24 hours after stopping heparin the pre-β band was again obvious on electrophoresis. A further lipoprotein effect was observed in these patients on prolonged therapy that was not seen after single injections of heparin: an increase of the α and diminution of the β fractions occurred and persisted for up to two weeks after stopping treatment. A similar change appeared in the serum of the patient with xanthomatosis, and has persisted subsequently during his continued heparin therapy (Fig. 7). This apparent shift of lipoprotein from β to α following heparin has been observed by Bolinger (1953), Nikkila and Grasbeck (1954) and others, but denied by Herbst *et al.* (1955). It appears from the present study that this change in distribution does not occur unless prolonged heparin therapy is administered.

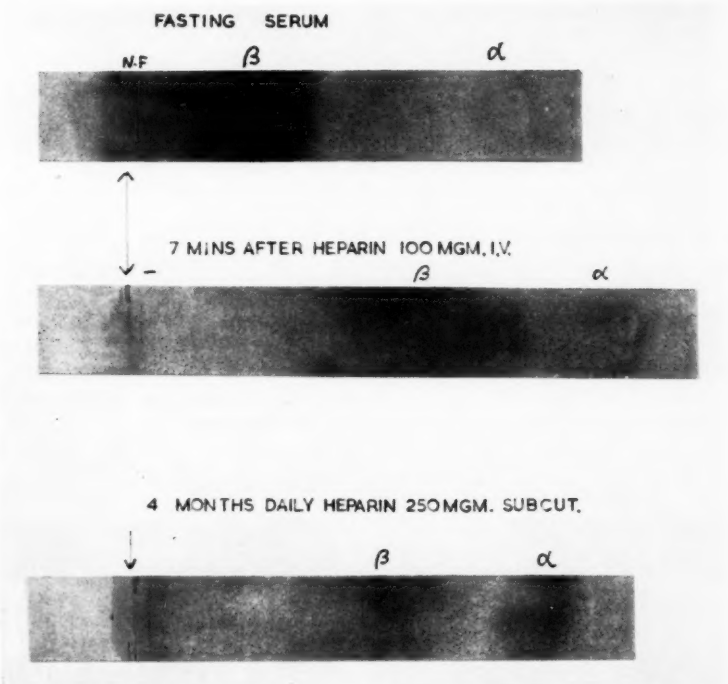


FIG. 7.—Diminution of β and increase of α lipoproteins after four months' daily heparin in a case of xanthomatosis.

Cholesterol. The serum cholesterol was reduced from 450 mg. per 100 ml. to 210 mg. per 100 ml. during heparin treatment in the patient with xanthomatosis alone, and furthermore the xanthomata showed a progressive reduction in size. Serum cholesterol was estimated by the Myers and Wardell technique. No significant change occurred in the serum cholesterol following single injections of heparin. The initial cholesterol levels were within normal limits in the three patients on prolonged heparin therapy and no change occurred during treatment.

Protamine. It has been reported that protamine antagonizes the effects of heparin on the lipoproteins (Brown, 1952; and Gruner, 1953). In the present study it was found that intravenous protamine sulphate modified the heparin changes but never completely abolished them. This is in accord with the results of Nikkila (1953). Protamine added in vitro had no antagonistic effect on the antilipæmic action of heparin.

Oleic Acid. The increased mobility of the lipoproteins following heparin has been ascribed to release of fatty acids following lipolysis by the clearing factor. The effects of oleic acid added to serum in vitro have been investigated by Gordon (1955). His findings have been confirmed in the present study. Within one minute of adding oleic acid, hypermobility of both β and α lipoproteins was apparent (Fig. 8), greater in degree than that seen following heparin.

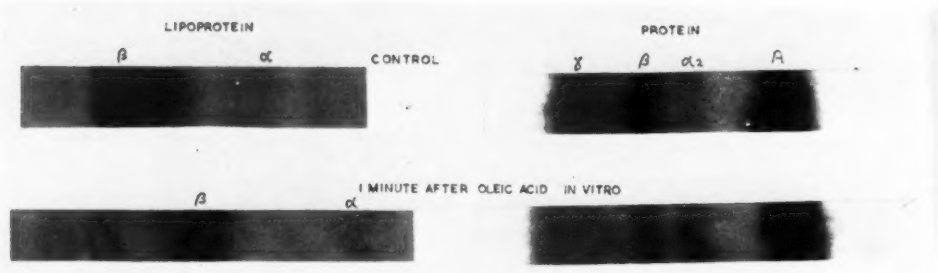


FIG. 8.—Increased mobility of lipoproteins following addition of oleic acid in vitro.

Incubation. Initial in vitro studies with heparin and protamine were carried out after incubation at 37°C. However it was found that the control serum also showed an altered lipoprotein distribution. Therefore subsequent in vitro heparin studies were conducted at room temperature, and the effects of incubation per se were investigated. Thirty sera were incubated at 37° for 2 to 24 hours. Eighteen of these showed increased migration of the β lipoprotein when compared with the same serum kept at room temperature (Fig. 9). This effect was comparable to that seen after heparin. It occurred within two hours in some cases, and remains unexplained. It is possible that hydrolysis or decomposition of the lipoproteins may have occurred.

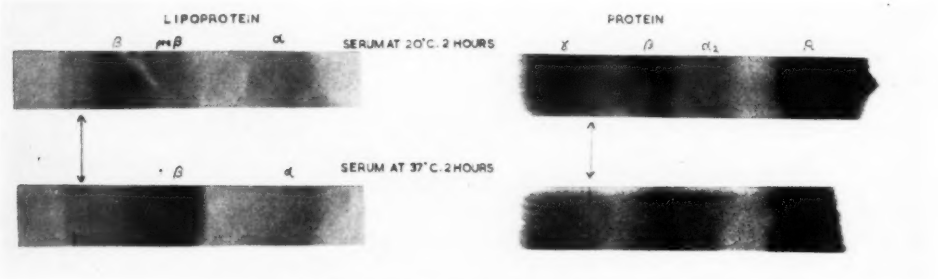


FIG. 9.—Increased mobility of β lipoprotein following incubation of serum at 37°C. for two hours.

DISCUSSION

Following systemic or in vitro heparin, various changes in lipoprotein pattern have been observed. The most consistent effect has been the disappearance of the pre-β lipoprotein which is apparently redistributed between the β and α lipoproteins. The action of heparin that results in

increased lipoprotein mobility and clearing of neutral fats has been ascribed to fatty acid release following hydrolysis of the triglycerides. Although it is probable that the pre-β fraction is affected by a similar mechanism, one-third of the cases showed an effect on this lipid alone unaccompanied by hypermobility of the other lipoproteins. It is possible that some other heparin action is responsible for this effect. The lipoprotein pattern produced by this selective effect of heparin closely resembled that found in the sera of some cases of acute infarction that had proved resistant to the antilipæmic action of heparin. It would be rash to attribute too great a significance to this resemblance of electrophoretic patterns, yet this refractory state might possibly be due to the previous secretion of an endogenous heparin-like substance. This resistance to heparin might also be explained by the release of an anti-heparin substance, or else by the lack of an intermediate compound necessary for the production of clearing factor following exogenous heparin. From earlier studies it is known that significant amounts of pre-β lipoprotein occur in the sera of patients with ischæmic heart disease. This lipid may be transiently cleared in some cases at the time of infarction, whereas it remains in others and also in those with acute coronary insufficiency. In the latter cases systemic heparin produces a marked effect on the lipoprotein pattern. It might be postulated that such patients have insufficient endogenous heparin or else that the release of this substance only occurs after massive cardiac infarction and necrosis of considerable amounts of cardiac muscle. Havel (1954) and Worley (1955) have made the interesting suggestion that an endogenous heparin may play a normal role in fat transport: reduction of this substance might explain the presence of excessive amounts of pre-β lipid in ischæmic subjects.

These findings suggest that patients with cardiac infarction may benefit from prolonged heparin therapy by virtue of the drug's anticoagulant action initially and its anti-lipæmic effect in smaller dosage thereafter. Unfortunately prolonged heparin therapy is not practicable for any large number of patients. Attempts are being made to find related compounds with the antilipæmic properties of heparin, yet free from anticoagulant activity (Constantinides *et al.*, 1954; and Besterman, 1957).

Summary

The lipoprotein patterns were compared in patients with various types of ischæmic heart disease. The distribution of the pre-β lipid alone was found to differ, being greater in cases of acute coronary insufficiency and abnormally diminished in those with acute cardiac infarction. Significant quantities of pre-β lipid subsequently appeared in these cases during recovery.

The effects of heparin on the lipoproteins were also studied: 10 per cent of the cases showed no change in lipid pattern, 54 per cent hypermobility of the lipoproteins, and 36 per cent reduction of the pre-β lipid without increased mobility of the β and α fractions. Increased migration of the lipoproteins also resulted from in vitro addition of heparinized serum, heparin, or oleic acid, or from incubation at 37° C. Prolonged heparin therapy was carried out in four patients, including one with xanthomatosis: redistribution of lipid between the β and α fractions occurred in these patients alone.

Acute cardiac infarction had occurred in 8 of the 11 heparin resistant cases and no pre-β lipid was present in their sera. This lipoprotein pattern resembled the selective heparin effect on this lipid seen after 36 per cent of heparin injections. It is possible that such patients may be refractory to exogenous heparin owing to previous endogenous heparin release.

Dr. Paul Wood, Director of the Institute of Cardiology, has unceasingly encouraged and advised me in this study and I am most grateful to him and to the other physicians of the National Heart Hospital for their kind co-operation. I am also indebted to the R.M.O and Registrars of the National Heart Hospital for their help. Dr. W. Dangerfield has, as always, given me invaluable criticism and advice. Miss B. Hall has provided the most patient technical assistance throughout this study. The heparin was supplied through the courtesy of Dr. E. V. B. Morton of Boots.

References

Anderson, N. G., and Fawcett, B. (1950). *Proc. Soc. exp. Biol.*, **74**, 768.
Anfinsen, C. B., Boyle, E., and Brown, R. K. (1952). *Science*, **115**, 583.
Besterman, E. M. M., and Evans, J. (1957). *Brit. med. J.*, **1**, 310.

Besterman, E. M. M. (1957). *Brit. Heart J.* **19**, 503
Bolinger, R. E., Grady, H. J., and Slinker, B. J. (1953). *Amer. J. med. Sci.*, **227**, 193.
Brown, W. D. (1952). *Quart. J. exp. Phys.*, **37**, 215.
Cairns, A. (1954). *Science*, **120**, 31.
Constantinides, P., Cairns, A., and Werner, A. (1954). *Arch. Int. Pharmacodyn.*, **99**, 334.
Dangerfield, W. G., and Smith, E. B. (1955). *J. clin. Path.*, **8**, 132.
Engelberg, H. (1955). *Amer. J. Phys.*, **181**, 309.
Gordon, R. C. (1955). *J. clin. Invest.*, **34**, 477.
Graham, D. M., Lyon, T. P., Gofman, J. W., Jones, H. B., Yankley, A., Simonton, J., and White, S. (1951). *Circulation*, **4**, 666.
Grossman, M. I., Moeller, H. C., and Palm, L. (1955). *Proc. Soc. exp. Biol.*, **90**, 106.
Grüner, A., Hilden, K., and Hilden, T. (1953). *Scand. J. clin. Lab. Invest.*, **5**, 241.
Hahn, P. F. (1943). *Science*, **98**, 19.
Havel, R. J., and Boyle, E. (1954). *Proc. Soc. exp. Biol.*, **85**, 468.
Herbst, F. S. M., and Hurley, N. A. (1954). *Jour. clin. Invest.*, **33**, 907.
——, Lever, W., Lyons, M. E., and Hurley, N. A. (1955). *J. clin. Invest.*, **34**, 581.
Herzstein, J., Chun-I Wang, and Adlersberg, D. (1954). *Ann. intern Med.*, **40**, 290.
Korn, E. D. (1955). *J. biol. Chem.*, **215**, 1.
Nikkila, E. (1953). *Scand. J. clin. Lab. Invest.*, **5**, suppl. 8.
——, and Grasbeck, R. (1954). *Acta. med. scand.*, **150**, 39.
Rosenberg, I. N. (1952). *Proc. Soc. exp. Biol.*, **80**, 751.
Smith, E. B. (1956). Ph.D. thesis, London.
Spitzer, J. J. (1952). *Amer. J. Phys.*, **171**, 492.
Worley, L. M., and Lequire, V. S. (1955). *Proc. Soc. exp. Biol.*, **89**, 181.

THE ELECTROCARDIOGRAM IN AORTIC STENOSIS

BY

ZAHIRA H. ABDIN*

From the Department of Medicine, Postgraduate Medical School, London

Received July 19, 1957

Many papers have recently appeared on aortic stenosis (Boas, 1935; Friedberg and Sohval, 1939; Kiloh, 1950; Lewes, 1951; Campbell and Kauntze, 1953; Mitchell *et al.*, 1954). The electrocardiographic findings have been described as those of left ventricular hypertrophy, often with a vertical heart position in pure stenosis (Kiloh, 1950). Assessment of the severity of aortic stenosis often presents difficulty. This study reports the electrocardiographic changes in aortic stenosis, and a comparison with those in left ventricular hypertrophy from other causes.

Methods and Material

Electrocardiograms were recorded either by an Elmqvist photographic machine or a Sanborn Visocardiette direct-writing instrument. Standard and unipolar limb leads, and unipolar chest leads were used (Goldberger, 1947).

Electrocardiograms from 44 cases of aortic stenosis were studied at Hammersmith Hospital. Twenty-five patients were living, of whom 8 had had an aortic valvotomy. In addition the cardiograms from 9 living patients published by Kiloh (1950), and Campbell and Kauntze (1953) were also examined. The remaining 19 records were taken from case notes of patients who had come to necropsy.

The ages of the 53 patients whose cardiograms were studied varied from 6 to 60 years. Thirty-seven were between 20 and 50. Fifteen cases were female and 38 male. Forty-four patients presented with a well established lesion with symptoms. Chest pain occurred in 40 per cent, syncopal attacks in 8 per cent, exertional dyspnœa of variable severity in 70 per cent, and nocturnal dyspnœa or congestive heart failure in 40 per cent. Measurements of the systolic upstroke time of the arterial pulse tracing were made in 9 cases, and in 4 of these the severity of the aortic stenosis was further assessed by the examination of the relationship between the systolic upstroke time and changes in pulse pressure.

Four cases with aortic stenosis also had mitral stenosis, and one of these had tricuspid stenosis also. The electrocardiograms of 19 living patients with coarctation of the aorta whose ages varied from 19 to 50 years were studied as controls for the living cases, while those of 15 autopsy subjects with hypertensive heart disease formed the control for the post-mortem series. None of the latter had any evidence of ischæmic heart disease at necropsy.

The criteria for voltage of R and S waves for left ventricular hypertrophy used were those set by Sokolow *et al.* (1949): R voltage in V5, 25 mm. or more; or R voltage in V5+S voltage in V1, 35 mm. or more; or R voltage in VL, 13·0 mm. or more when the heart is horizontal; or R voltage in VF, 20 mm. or more when the heart is vertical.

Results

Aortic Stenosis (*living series*). Five cases showed extremely high voltage; these all had severe lesions with well established symptoms. ST–T wave changes were also studied. The two cases

* Present address: Children's Hospital, Kasr-el-Aini University Hospital, Cairo.

with bundle-branch block were not included. T wave inversion in left ventricular leads was present in 31 out of 32 cases. It was deep (over 5 mm.) in 16, moderate (3–5 mm.) in 14, and slight (less than 3 mm.) in one case (Table I). The correlation between symptoms and severity

TABLE I

INCIDENCE AND DEGREE OF T WAVE INVERSION IN AORTIC STENOSIS AND IN CONTROLS WITH COMPARABLE DEGREES OF VENTRICULAR HYPERTROPHY

T inversion	Aortic stenosis, 19 autopsy cases (excluding 4 with bundle-branch block), 15 cases	Aortic stenosis, 34 living cases (excluding 2 with bundle-branch block), 32 cases	Hypertensive without ischæmia, 15 cases (excluding 1 with bundle-branch block), 14 cases	Aortic coarctation, 19 cases (excluding 3 normal EC.) 16 cases	Hypertensive and ischæmic disease, 4 cases
Deep	10	16	1	1	3
Moderate	4	14	2	3	
Slight	0	1	4	4	
Absent	1	1	7	8	1
Total incidence ..	14	31	7	8	3

seemed to be close. Thus a boy of 17 years had normal exercise tolerance and no chest pain, his only symptom being occasional syncope; the systolic upstroke time of the femoral arterial pulse was 0·15 sec. (indicative of mild to moderate stenosis) and there was no T wave inversion (Fig. 1). Conversely a woman, aged 22 years, had had frequent chest pain since the age of 13, and had progressively increasing exertional dyspnœa; the systolic upstroke time was 0·24 sec. (indicating severe stenosis) and the electrocardiogram showed deeply inverted T waves (8 mm.) (Fig. 2). Table II illustrates the direct relationship between T wave inversion and systolic upstroke time in the 9 cases in which the latter was measured. T wave changes may precede the onset of symptoms.

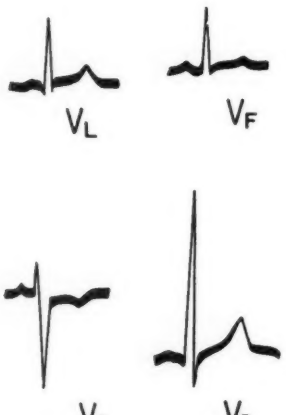


FIG. 1.—Facsimile cardiogram from a patient with mild aortic stenosis without symptoms. RV5=31 mm. T wave normal.

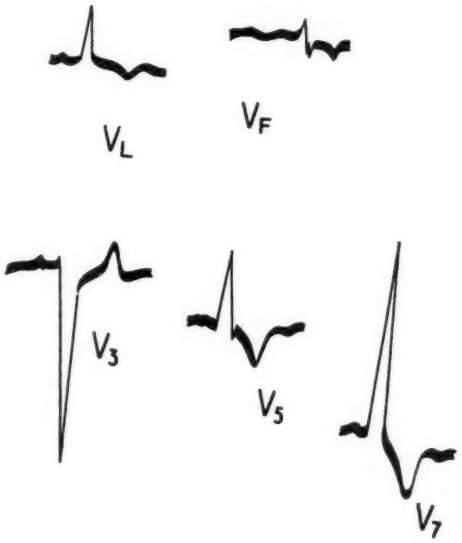


FIG. 2.—Cardiogram from a patient with severe aortic stenosis with frequent angina. RV5=14 mm.; RV7 =32 mm.; TV5 is inverted (6 mm.); TV7 is inverted (8 mm.).

TABLE II
RELATION OF T WAVE INVERSION TO TIME TO PEAK OF FEMORAL ARTERIAL PULSE WAVE

Case No.	Time to peak (Tp) sec.	T wave inversion T (millimetre)
1	0·15	0
2	0·16	0
3	0·18	4
4	0·22	6
5	0·22	6
6	0·22	6
7	0·24	8
8	0·24	8
9	0·25	10

Tp=Time to peak in seconds measured on the arterial femoral pulse tracing.
T=Inversion of the T wave in left ventricular leads in millimetres.

Moderate to deep T wave inversion in V3 or V4 was present in 6 cases, and a biphasic T wave in V3 was present in 7 others. Although the patients with extreme voltage changes usually showed the deepest inversion of the T wave, in 2 instances there was T wave inversion (slight to moderate inversion in V5 or V7) with no increase in voltage of the QRS complexes. There was only one example of voltage being increased without associated T wave changes.

Depression of the S–T segment in left ventricular leads of 1–2 mm. occurred in 24 cases. In right ventricular leads S–T elevation (1–3 mm.) occurred in 22 electrocardiograms, and the T wave was upright in 24. One patient showed right bundle-branch block and one left bundle-branch block, while the P–R interval was over 0·2 sec. in 4 instances. Atrial fibrillation was not seen in the cases of isolated aortic stenosis, but was present in the three subjects with combined aortic and mitral valve stenosis. The Q–T ratio was normal.

The heart position was vertical in 17 of the 34 patients.

COARCTATION OF THE AORTA

Three patients with coarctation of the aorta had normal tracings. The other 16 had voltage changes of left ventricular hypertrophy, of moderate degree in 11, and extreme in 5. T wave inversion was present in only 8 of the 16 cases with voltage changes. The inversion was minimal in 4, slight to moderate (3 mm.) in 3, and deep (6 mm.) in only one (Fig. 3 and Table I). No inversion was seen in V3. S–T depression of 0·5–1·5 mm. was present in four cardiograms. In the right ventricular leads the T wave was upright, and there was S–T segment elevation of 0·5–1·5 mm. in 13 out of the 16 cases.

The mean values for R wave voltage and T wave inversion in the left ventricular leads (V5 or V7), and the mean ratio R voltage/T inversion in the cases with T wave inversion in the same leads, are compared for cases with aortic stenosis and cases with coarctation in Table III. It is clear that although the voltage of the R wave in the two groups is comparable, the T wave inversion in the patients with aortic stenosis is much greater than in those with coarctation. This is reflected in the much larger ratio R/T in the coarctation series than in those with aortic stenosis.

In one patient with coarctation the P–R interval was 0·24 sec., while none had bundle-branch block or arrhythmias. The Q–T ratio was normal. A vertical heart position was present in 10 out of 16 patients.

THE RELATIONSHIP BETWEEN CARDIOGRAPHIC CHANGES AND POST-MORTEM FINDINGS IN AORTIC STENOSIS AND IN HYPERTENSION

Left ventricular thickness and cardiographic voltage changes. At autopsy all the patients with aortic stenosis had left ventricular hypertrophy, the thickness of the left ventricle varying from

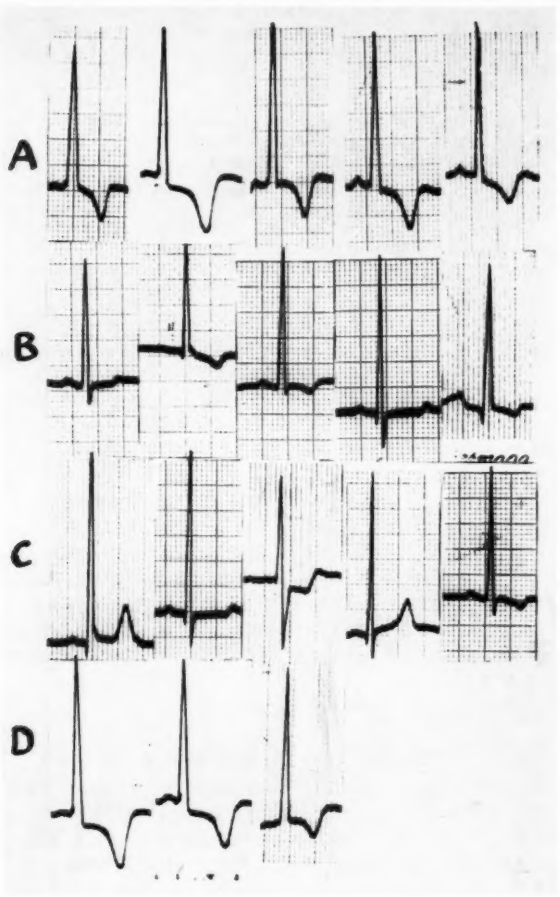


FIG. 3.—Multiple examples of left ventricular leads (V5 or V7) from aortic stenosis (A), coarctation (B), hypertension without coronary artery disease (C), and hypertension with ischæmic heart disease (D).

16 to 30 mm. All those with hypertension had left ventricular hypertrophy, the left ventricular thickness ranging from 18 to 25 mm. Most of the ventricles in hypertension had a thickness of 22–25 mm., while in most of the aortic stenosis cases the thickness was 20–22 mm. The average thickness in the two groups was 21 mm. for the aortic stenosis cases and 22 mm. for those with hypertension. Cardiographic voltage changes of left ventricular hypertrophy were present in all but one case of aortic stenosis, and all but one of the hypertensive subjects.

T wave inversion, left ventricular thickness, and aortic valve size. For comparable degrees of left ventricular hypertrophy, T wave inversion in left ventricular leads was much more frequent and more remarkable in the patients with aortic stenosis (Tables I and III). The frequency of deep T wave inversion (5 to 10 mm.) in the aortic stenosis series (10 out of 15 cases), and the scarcity of such deep T waves in the hypertensive cases (1 out of 14 cases), is particularly striking (Fig. 3C and Table I).

TABLE III

COMPARISON OF MEAN VALUES FOR VOLTAGE, LEFT VENTRICULAR THICKNESS, AND T WAVE INVERSION IN AORTIC STENOSIS AND CONTROLS

	Aortic stenosis (P.M.)	Aortic stenosis (living)	Hypertension	Coarctation
R*	19·5	19·8	20·0	22·4
V	21·0	—	22·2	—
T	4·8	4·1	1·2	2·4
R/T†	3·4	4·7	12·2	14·7

R=Voltage of R wave in lead V5 (mm.).
V=Thickness of left ventricle (mm.).
T=Inversion of T wave in lead V5 (mm.).
R/T=Ratio of mean voltage of R wave in lead V5 (mm.) to mean T inversion in lead V5 (mm.) for cases with T wave inversion in lead V5.

* Includes cases with and without T wave inversion.
† Includes only cases with T inversion.

Four other hypertensive cases were excluded because there was histological evidence of ischæmic heart disease. It is of interest that three of these had deeply inverted T waves of the type seen in aortic stenosis (Fig. 3D).

T wave inversion in the hypertensive patients occurred only in those who showed the maximum degrees of left ventricular hypertrophy. In the aortic stenosis patients the deeply inverted T waves again were usually but not always associated with the greater degrees of left ventricular hypertrophy. There was, however, a close relationship in the aortic stenosis patients between the degree of T wave inversion and valve size when this was measured at necropsy.

Three cases had only slight to moderate T wave inversion with a severe degree of aortic stenosis: two had cardiographic evidence suggestive of small myocardial infarctions with post-mortem evidence of macroscopic infarctions, and the third had bundle-branch block of indeterminate type. The incidence of inverted T waves in V5 and V6 in all groups is shown in Table I, cases with bundle-branch block being excluded. Of the 19 patients with aortic stenosis, one had right and two left bundle-branch block and one had a bundle-branch block of undetermined type. In all the lesions were severe. By contrast, only one of the 15 patients with hypertension had left bundle-branch block. In the presence of bundle-branch block there was no evidence of calcification of the bundle of His.

Of the 12 patients with aortic stenosis in sinus rhythm, one had a P–R interval longer than 0·2 sec. None of the hypertensive cases had a prolonged P–R interval. Atrial fibrillation was present in 7 instances of aortic stenosis: only one of these had mitral stenosis also. Atrial fibrillation occurred in two patients with hypertension. Ventricular ectopic beats were frequent in aortic stenosis, but not seen in the hypertensive cases. The Q–T ratio was normal in all groups.

The ratios between left ventricular and right ventricular thickness were examined in relation to vertical heart position and clockwise rotation. Seven patients with aortic stenosis and 6 of those with hypertension had a vertical or semivertical heart position, but only 4 of the former and 3 of the latter had right ventricular hypertrophy.

Extreme degrees of clockwise rotation of the heart with S>R or S=R in V5 (Pagnoni and Goodwin, 1952) were present in 6 cases with aortic stenosis and 3 with hypertension (Fig. 4). All had pathological evidence of right ventricular hypertrophy. However, right ventricular hypertrophy without clockwise rotation was present in 6 with aortic stenosis and in 4 with hypertension.

It is of interest to note that in 70 normal adult patients of all ages examined the electrocardiogram showed a vertical or semi-vertical electrical position of the heart in over one-third, while none had gross clockwise rotation with S>R in V5.

The incidence of deeply inverted T waves in other cases of left ventricular hypertrophy was also

studied. Thirty patients were examined; they were mainly adults; 15 had aortic incompetence, 8 had patent ductus arteriosus, and 7 had ventricular septal defects. Only 2 cases among all the groups had a deeply inverted T wave 6 mm. in depth in V5 or V6. One was a child of 9 years with a septal defect, and the other was aged 17, and had free aortic incompetence and extreme enlargement of the left ventricle.

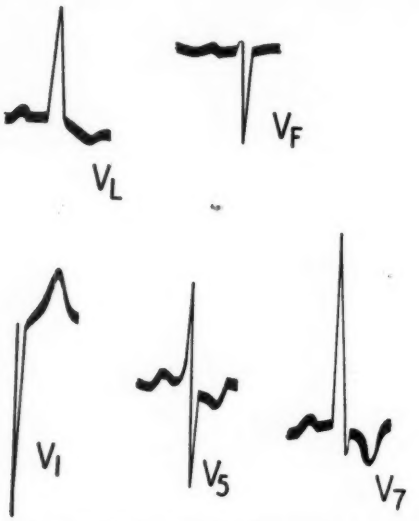


FIG. 4.—Facsimile cardiogram from a case of aortic stenosis, showing biventricular hypertrophy. There is clockwise rotation (R/S ratio=1 in V5) and a horizontal heart position with high voltage of R in V7 (33 mm.) and T wave inversion. The left ventricular thickness was 25 mm., while the right ventricular thickness was 8·0 mm. at necropsy.

DISCUSSION AND CONCLUSIONS

The most striking cardiographic abnormality in patients with aortic stenosis is inversion of the T wave in the left ventricular leads (Fig. 3, Tables I and III). The inversion is often deep and is almost invariably present when the voltage in these leads is high. On occasion, T wave inversion may occur without increased voltage. The T wave changes are in striking contrast to the findings in coarctation of the aorta, in hypertension without associated ischæmic heart disease, and in other conditions causing left ventricular hypertrophy in which T wave inversion is often not striking (Fig. 3). However, when hypertension is associated with ischæmic heart disease T wave inversion similar to that in aortic stenosis occurs. A deeply inverted asymmetrical T wave in left ventricular leads in the absence of coronary artery disease is highly suggestive of aortic stenosis. It is probable that the voltage changes commonly seen in conditions causing left ventricular hypertrophy are the result of the increased mass of the left ventricular muscle. However, deep inversion of the T wave is usually associated with ischæmic myocardial changes rather than with increase in muscle thickness. The frequency of these changes in aortic stenosis suggests the presence of ischæmic changes in the myocardium, either as a result of associated coronary artery disease or of impaired coronary blood flow resulting from the valvular obstruction. In favour of the latter hypothesis is the fact that deep T wave inversion occurs in children and adolescents with aortic stenosis, in whom coronary disease is unlikely to be present. Furthermore, cardiographic appearances suggestive of infarction are not infrequent in the second and third decade (Fig. 5 and 6). Similar changes have been reported by Friedberg and Sohval (1939). Deep inversion of the T wave in patients over 20 years may occur in the transitional zone as well as in left ventricular leads, suggesting septal ischæmia (Fig. 7). A positive effort test was present in three patients with aortic stenosis studied in this series. The relative frequency in aortic stenosis, compared with other causes of left ventricular hypertrophy as gauged from the present work as well as from previous records (Mitchell *et al.*, 1954; Lewes, 1951), of bundle-branch block, of prolongation of the P–R interval, and of atrial fibrillation also lend support to the suggestion that ischæmia is common in this disorder. It is of interest that the patients with left bundle-branch block had severe stenosis, but no gross evidence of calcification in the conducting tissue was found at necropsy. Friedberg and Sohval (1939) have reported that transient bundle-branch block may occur in aortic stenosis.

Supporting clinical evidence of ischæmia is derived from the frequency of anginal syndromes in aortic stenosis. Perhaps the strongest evidence that T wave inversion is not directly related to the degree of left ventricular hypertrophy is the rarity of deep T wave changes in coarctation of

the aorta or hypertension even when these had left ventricular hypertrophy of a degree that, if present in aortic stenosis, was almost always accompanied by deep inversion of the T wave (Fig. 3). Furthermore T wave inversion in aortic stenosis may precede voltage changes (Campbell and Kauntze, 1953). The findings at necropsy also tend to support the primary ischæmic theory. Thirteen patients with aortic stenosis were found to have myocardial infarction or scattered areas of ischæmic fibrosis with patent coronary arteries and minimal or no atheroma. Of these, 3 had

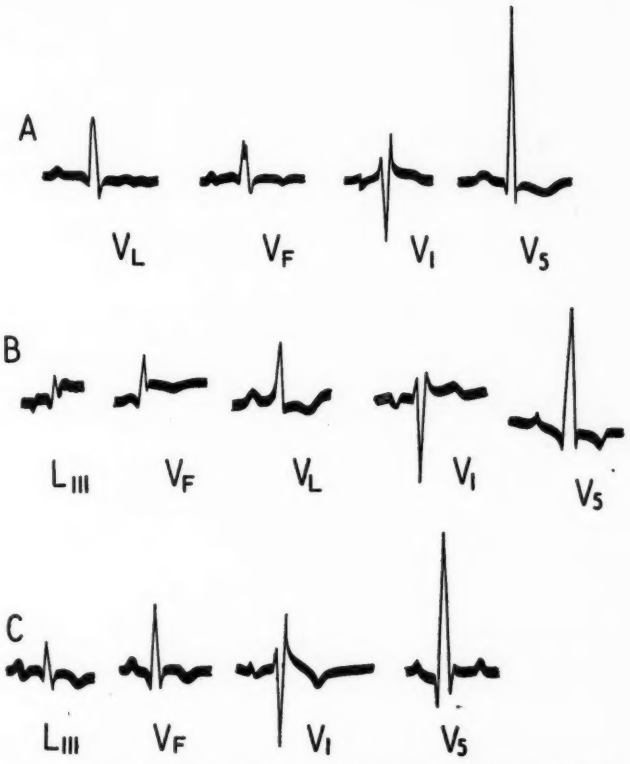


FIG. 5.—Facsimile cardiogram from a patient with aortic stenosis, aged 19 years. These three tracings were taken over a three-month period. In (B) small Q waves and S–T elevation are seen in leads III and VF. T in V1 is upright while T in V5 is inverted (3·0 mm.). In (C) T in V1 is inverted while T in V5 is upright. Appearances suggest the development of a posterior infarction in (B).

recent infarctions, 4 old infarctions, and 9 numerous microscopic areas of fibrosis presumably ischæmic in origin. Wigle (1957) has charted the areas of fibrosis in four cases and found them to be widespread with some predilection for the posterolateral region, and this site corresponds to the site of T wave inversion in the cardiogram. The relative infrequency of large Q waves in the electrocardiogram may be related to the small size of the areas of fibrosis and to the relative infrequency of large areas of infarction. The mechanism of the myocardial ischæmia is still uncertain. Green (1936) demonstrated a significant reduction in the minute volume flow through the coronary arteries and found that the flow could not easily be increased. Encroachment of the coronary orifices by calcification and fibrosis, the slow rise of the arterial pulse, acceleration

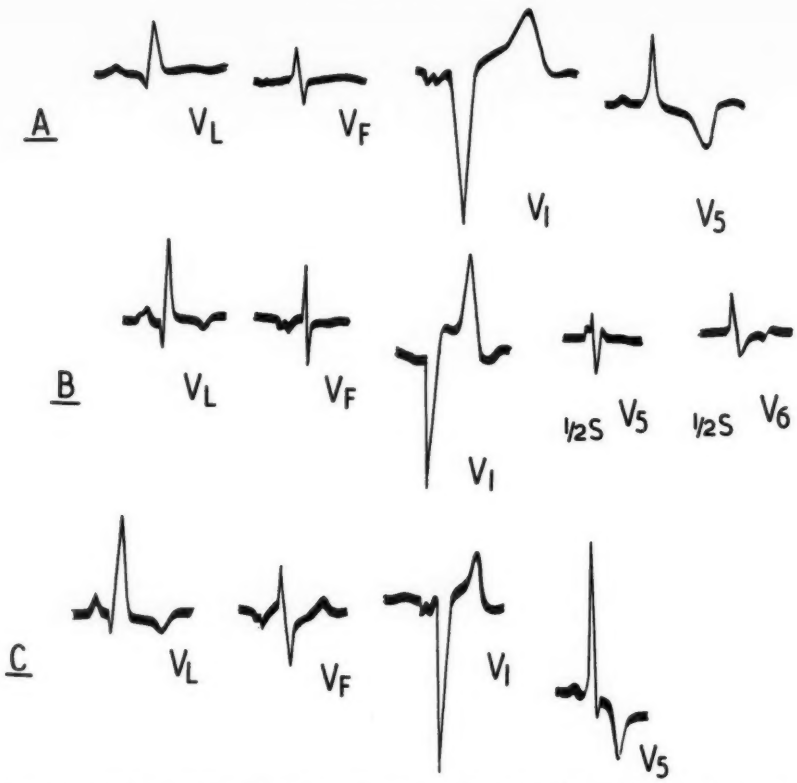


FIG. 6.—Facsimile cardiogram from a patient, aged 34 years, with aortic stenosis. These three tracings were taken over a three-month period. The appearance in (B) (Q waves 5 mm. in VL with inversion of the T waves and R/S ratio in V5 less than unity) suggests the development of an anterolateral infarction and/or associated right ventricular hypertrophy [½S=half sensitivity].

of blood past the coronary orifices tending to produce a suction effect, and low pulse pressure may be all in part contributing factors.

The inverted T wave in left ventricular leads may also be of value in the assessment of the severity and the prognosis of aortic stenosis, for they may precede other signs and symptoms of aortic stenosis; furthermore they seem to bear a fairly close relationship to valve size. For example, T wave inversion 5 mm. or more in chest leads was usually associated in this series with a valve circumference 3 cm. or less (Fig. 7 and 8). It is of interest that there is a correlation between the depth of T wave inversion and the duration of the maximal ejection phase of ventricular systole as estimated by the time from the onset to the peak on the peripheral arterial pulse tracing (Table II).

A vertical electrical position in the cardiogram was common in less advanced aortic stenosis as well as in coarctation, but was less frequently found among the series studied after necropsy. The reason for this is not clear. The presence of associated right ventricular hypertrophy does not seem likely to be the factor responsible, for right ventricular hypertrophy is likely to be more common in advanced cases than in the less severe ones. Furthermore, half those with a vertical position shown electrocardiographically had no right ventricular hypertrophy, while less than half of those with right ventricular hypertrophy had shown a vertical position on the electrocardiograph.

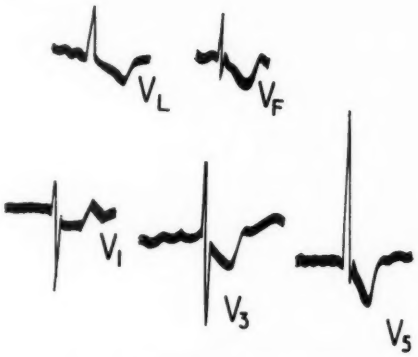


FIG. 7.—Facsimile cardiogram from a patient, aged 48 years, with aortic stenosis. Systolic upstroke of arterial pulse wave was 0·22 sec., and gradient across the aortic valve was 120 mm. Note: R in V5= 30 mm.; deeply inverted T in V5=8 mm.; inverted T in V3 and intermediate heart position.

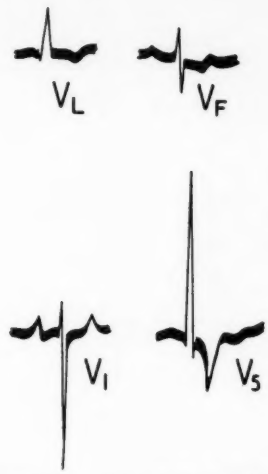


FIG. 8.—Facsimile cardiogram of a patient with severe aortic stenosis, showing high voltage of R (29 mm.) and deep T wave (10·0 mm.) inversion, in V5 and horizontal heart position.

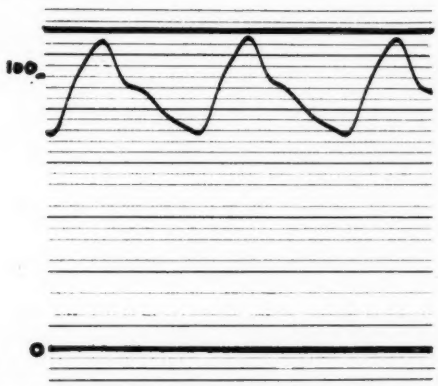


FIG. 9.—Femoral pulse tracing of the same patient. The author has omitted the time-marking but the time of the peak of the wave was 0·25 sec. The calibration is 10 mm. on the tracing = 20 mm. Hg actual pressure, so that this was 115/80 mm.

The present study has confirmed the report of Pagnoni and Goodwin (1952) that clockwise rotation in the presence of electrocardiographic evidence of left ventricular preponderance, suggests the presence of associated right ventricular hypertrophy. Using their criteria for clockwise rotation, all with this sign had associated right ventricular hypertrophy. However, of those with right ventricular hypertrophy less than half showed clockwise rotation.

SUMMARY

Cardiograms from 34 living patients with aortic stenosis have been compared with those of 19 with coarctation of the aorta.

Cardiograms from 19 patients with aortic stenosis who came to necropsy have been compared with those of 15 hypertensive subjects presenting no evidence of ischæmic heart disease at necropsy.

Although the voltage changes in all groups were comparable, T wave inversion was more frequent and of greater magnitude in aortic stenosis than in hypertension or coarctation of the aorta, and was of value in the diagnosis of aortic stenosis.

The depth of T wave inversion bore a close relationship to the severity of the stenosis of the aortic valve and was of value in clinical assessment.

Evidence is given to show that the T wave inversion in aortic stenosis is ischæmic in origin and due to poor coronary flow rather than to coronary artery disease.

Atrial fibrillation and bundle-branch block were late manifestations, but first degree heart block occurred early in the disease.

A vertical heart position was common in aortic stenosis and in coarctation of the aorta. It was much less frequent in the more advanced cases of aortic stenosis and therefore not necessarily related to associated right ventricular hypertrophy. By contrast extreme clockwise rotation ($R<S$ in V5) in aortic stenosis was likely to be due to associated right ventricular hypertrophy.

I am deeply indebted to Dr. J. F. Goodwin and to Dr. A. E. Doyle for assistance with this work. I also wish to thank Prof. C. V. Harrison for his help and for permission to examine necropsy material, and Dr. E. D. Wigle for permission to cite his detailed necropsy studies. Dr. G. H. Neilson kindly provided data on arterial pulse tracings in aortic stenosis.

References

Boas, E. P. (1935). *Amer. J. med. Sci.*, **190**, 376.
Campbell, M., and Kauntze, R. (1953). *Brit. Heart J.*, **15**, 179.
Friedberg, C. K., and Sohval, A. R. (1939). *Amer. Heart J.*, **17**, 452.
Green, H. D. (1936). *Amer. J. Physiol.*, **115**, 94.
Goldberger, E. (1947). *Unipolar Lead Electrocardiography*. Henry Kimpton, London.
Kiloh, G. A. (1950). *Brit. Heart J.*, **12**, 33.
Lewes, D. (1951). *Brit. med. J.*, **1**, 211.
Mitchell, A. M., Sackett, C. H., Hunzicker, W. J., and Levine, S. A. (1954). *Amer. Heart J.*, **48**, 684.
Pagnoni, A., and Goodwin, J. F. (1952). *Brit. Heart J.*, **14**, 450.
Wigle, E. D. (1957). Personal communication.

THE ELECTROCARDIOGRAM IN PULMONARY EMBOLISM

BY

ROBERT H. CUTFORTH AND SAMUEL ORAM

From King's College Hospital

Received May 9, 1957

The importance of the electrocardiogram in the diagnosis of pulmonary embolism was first demonstrated by McGinn and White (1935) but general opinion still varies concerning the precise diagnostic value of this method of investigation. As recently as 1952 Newman stated that in only 10–20 per cent of cases of pulmonary embolism is there a characteristic pattern and that electrocardiographic examination is not a good method of making the diagnosis. By contrast, Phillips and Levine (1950) are of the opinion that the diagnosis of pulmonary embolism can be made with a high degree of accuracy and, indeed, that the first clue to the diagnosis may often be found by this method.

The object of this paper is to analyse in detail the electrocardiograms of 50 undoubted cases of pulmonary embolism and to compare these results with those of other workers in order to assess its value in making the diagnosis. In addition, an attempt is made to correlate the severity of the clinical picture with the electrocardiogram, and also to show how the presence or absence of pulmonary infarction affects it.

Material and Method of Selection

The material was obtained from the records of four hospitals. About a quarter of the cases were seen personally by one of us within 24 hours of the time at which the embolism occurred. All patients had at least one 12-lead electrocardiogram (the three standard leads, the three unipolar limb leads, and six chest leads, V1–6) taken after the embolism and in 25 instances serial records were obtained.

In a study of this kind there are two practical difficulties in obtaining suitable material. The first is to obtain records from patients in whom there is no doubt whatsoever concerning the certainty of the diagnosis. This is discussed below and our diagnostic criteria are given. The second difficulty is that those patients who die very soon after the onset of the embolism frequently do so before there is time for an electrocardiogram to be taken. In this series of 50 patients there are 11 in whom the diagnosis was verified after death. The post-mortem examinations revealed that the coronary arteries were patent in all except Case 43, and this case is discussed separately.

Details of the 11 cases that came to autopsy can be seen in Table I.

In addition to the autopsied cases we studied 83 other patients in whom a clinical diagnosis of pulmonary embolism had been made but we discarded 44 of these because, in our opinion, the clinical picture was not certain enough to put the diagnosis beyond all doubt. The remaining 39 patients were considered by us to be undoubted examples of pulmonary embolism, our criteria being as follows.

Twenty-one suffered a sudden attack of pleuritic pain followed in a few days by hæmoptysis. This attack occurred either within 14 days of a surgical operation or in the presence of a recent venous thrombosis. In none of them did we find any cause other than pulmonary embolism that could explain the clinical picture. In addition, every patient in this group had either

TABLE I

SUMMARY OF FINDINGS IN PATIENTS AT NECROPSY

Case No.	Clinical findings	Post-mortem findings	Survival	Time of EC.	EC. findings			
					RBBB	S1 Q3 T3	RVT*	Other
40	F. 67. Sudden syncope and fall in B.P. JVP+	R.L.L. infarct. Congestive failure. Femoral thrombosis.	13 days	12 hours	RBBB	—	—	—
41	M. 50. Post-operative. Sudden syncope and fall in B.P.	Main P.A. blocked and multiple small pulm. emboli.	1 day	8 hours	—	S1 Q3 T3	RVT↓	S–T depr.
42	M. 54. Chronic cor pulmonale. Sudden syncope and fall in B.P.	Massive infarction R. lung. Multiple infarcts L. lung. Embolus in R.P.A.	5 days	2 days	RBBB	S1 Q3 T3	—	—
43	M. 66. Myocardial infarct 2 years previously. Pleural pain and hæmoptysis one week. Sudden syncope.	Cardiac infarcts, old and recent. Multiple recent pulmonary infarcts. Emboli in both P.A.	4 days	2 days and 3 days	— RBBB	S1 Q3 T3 —	— —	Arrhythmia —
44	F. 58. Post-operative. Sudden syncope and fall in B.P.	Carcinoma sigmoid colon and pelvic abscess. Two abscesses in L.U.L. Organizing embolus in artery to L.U.L.	23 days	5 days 14 days 21 days	— — —	— T3 T3	RVT↓ RVT↓ RVT↓	— — —
45	F. 68. After pneumonia. Sudden syncope, fall in B.P., JVP++.	Bilat. bronchopneumonia. Embolus impacted in R. and L. P.A.	1 hour 30 min.	1 hour 20 min.	RBBB	—	RVT↓	—
46	M. 52. Post-operative. Sudden dyspnœa. No pain. JVP+. Triple rhythm.	Bilat. saphenous vein thrombosis. Coiled clot in the L.P.A.	2 days	12 hours	RBBB	S1 Q3 T3	RVT↓	—
47	F. 84. Diabetic precoma. Sudden dyspnœa and fall in B.P.	Multiple pulmonary emboli and thrombosis of both P.A.	10 days	3 days	—	S1 T3	RVT↓	
48	F. 74. Venous thrombosis R. leg 14 days previously. Sudden dyspnœa and JVF+. 8 days later sudden syncope.	Embolus blocking bifurcation of P.A. R. ext. iliac thrombophlebitis.	13 days	1 day 6 days	—	S1 T3 Less	—	S–T depr. Less
49	M. 51. Fract. fibula in plaster 23 days previously. Sudden syncope, fall in B.P., triple rhythm. JVP+.	Embolus blocking main P.A.	1 day	6 hours	RBBB	S1 Q3 T3	—	—
50	F. 75. Sudden dyspnœa 2 weeks before admission. Triple rhythm. JVP+.	Firmly adherent embolus in R.P.A.	22 days	21 days	RBBB	S1 T3	—	—

* =Right ventricular T wave inversion.

abnormal physical signs in the chest or X-ray findings supporting the diagnosis of pulmonary infarction (Short, 1951).

Of the remaining 18, the pulmonary embolism occurred within 14 days of a surgical operation in 12 and in the presence of venous thrombosis in the legs in the other 6 patients. Cases 23 to 28 suffered sudden attacks of pleuritic pain and were later found to have physical signs or an X-ray appearance suggestive of pulmonary infarction. Cases 29, 30, 31, 32, 35, and 39 suffered attacks of syncope and were later found to have physical signs or X-ray signs suggestive of pulmonary infarction. Cases 22 and 23 complained of a sudden gripping pain in the chest which was later followed by hæmoptysis. Case 34 had a sudden attack of syncope which was later followed by hæmoptysis. Cases 36 and 37 had sudden attacks of syncope with a fall in blood pressure and elevation of the jugular venous pressure. Case 38 complained of a gripping pain in the chest which was rapidly followed by syncope with a fall in blood pressure.

Sex Distribution. The sex distribution was equal in this series, 25 men and 25 women.

Age Incidence. The age distribution in 10-year periods was 15–24, 1; 25–34, 3; 35–44, 4; 45–54, 10; 55–64, 14; 65–74, 16; 75–84, 2. Although the average age was about 60 years or slightly older, the statement that pulmonary embolism is rare under 40 is not borne out, as seven were so.

Clinical Severity of the Cases. It is well recognized that while some patients with pulmonary embolism may suffer severe disturbances of the circulation, giving rise to the classic picture of acute cor pulmonale as described by White (1935), commonly associated with such obvious clinical clues as dyspnœa, cyanosis, pain in the chest, hæmoptysis, and pyrexia, many patients, in fact, do not show these features. Barnes (1937) was the first to point out that the important clinical signs of pulmonay embolism are not cyanosis and dyspnœa but shock, collapse, tachycardia, and a fall in blood pressure.

In order to discover whether there were any differences in the electrocardiographic findings in the two clinical types, we divided our material into two groups according to the clinical findings. Cases were judged to be severe when there was syncope, fall in blood pressure, triple rhythm, elevation of the venous pressure, or any combination of these signs. Twenty-eight patients were so classified, and in the remaining 22, which we have called the non-severe group, none of these signs was observed.

Electrocardiographic Findings in Pulmonary Embolism

McGinn and White (1935) described the electrocardiographic changes found in the standard leads in seven cases of acute cor pulmonale resulting from pulmonary embolism. The changes they described were (*a*) a prominent S wave and low origin of the T wave in standard lead I; (*b*) the gradual " staircase " ascent of the S–T segment in lead II; and (*c*) a Q wave and late inversion of T in lead III. In two cases they also described the changes found in lead IV, a bipolar lead from the front and back of the chest.

Next, Barnes (1937) drew attention to the shift to the right in the electrical axis of the heart, and Durant *et al.* (1939) showed that transient right bundle-branch block patterns could result from this condition.

Wood (1941) found that the T wave became inverted in lead IVR and in certain other bipolar chest leads following pulmonary embolism, and it soon was clearly established that it is the T wave recorded from those præcordial electrodes facing the right ventricle that may be commonly inverted. This is discussed later.

Since the introduction of the so-called unipolar leads, much attention has been paid by Wilson, Rosenbaum and Johnston (1947), Eliaser and Giansiracusa (1952) and Goldberger (1953) to the alteration of the electrical position of the heart. The commonest finding has been clockwise rotation of the heart about the long axis, and alteration of the electrical axis towards the vertical position is only slightly less common.

The finding of a peaked P wave or " P pulmonale " was discussed by Katz (1946). Wood (1948) found it only occasionally in massive pulmonary embolism while Eliaser and Giansiracusa

TABLE II

ELECTROCARDIOGRAPHIC ABNORMALITIES OCCURRING IN PULMONARY EMBOLISM

Electrocardiogram in 50 cases	Number of cases	Number classed as severe
i. Sinus tachycardia	34	24
ii. Alteration of electrical position (*a*) Vertical	33	23
(*b*) Clockwise rotation	30	20
iii. S1 Q3 T3 pattern	14	11
iv. S1 T3 changes	4	3
v. T3 inversion	9	7
vi. QVF	10	6
vii. T wave changed in VF	23	17
viii. S–T segment depression	9	8
ix. Right ventricular T wave inversion	23	19
x. Right bundle-branch block patterns	7	7
xi. Alteration of cardiac rhythm	7	3
xii. P wave abnormalities	6	4

(1952) regard it as a grave prognostic sign. The latter also describe the occurrence of auricular arrhythmias resulting from pulmonary embolism.

The difficulties encountered in distinguishing electrocardiographic patterns found in posterior myocardial infarction from those resulting from pulmonary embolism have been discussed by Barnes (1937), Horn *et al.* (1939), Sokolow *et al.* (1940), Phillips and Levine (1950), and Goldberger (1953). This problem is considered below under differential diagnosis.

ANALYSIS OF THE ELECTROCARDIOGRAPHIC FINDINGS IN THIS SERIES OF CASES

We have found that there are 12 different electrocardiographic changes that may occur, either singly or in combination, in cases of pulmonary embolism (see Table II). These 12 signs are apt to occur in particular combinations that give rise to 8 recognizable patterns, 3 of which are highly diagnostic.

The 12 changes, their frequency and duration, are as follows:

(i) *Sinus Tachycardia.* This is recognized as a frequent, if not invariable accompaniment of pulmonary embolism (Fig. 1). The total number of patients showing a tachycardia of 90 a minute or more was 34. The true figure is undoubtedly higher, however, as several of the electrocardiograms were taken many days after the embolism, and of 22 patients in whom it was taken within 48 hours of the embolism 19 showed a ventricular rate of 90 a minute or more. All these 19 patients were in the severe group. Of the three patients with records taken within 48 hours but not showing tachycardia, Case 46, which was also a severe case, showed a paroxysm of beats at 150 a minute in one lead. In the other two patients (Cases 3 and 6) the electrocardiograms were virtually normal and showed no evidence suggestive of pulmonary embolism. Both these cases were in the non-severe group.

(ii) *Alteration of the Electrical Position of the Heart.* Both alteration of the electrical axis of the heart towards the vertical position and clockwise rotation of the heart about its long axis as viewed from below have frequently been reported in cases of pulmonary embolism. McGinn and White (1935) noted that none of their cases showed left axis deviation. Kuo and Vander Veer (1950) pointed out that alteration in the electrical axis may be an early and transient phenomenon. Phillips and Levine (1950) mention the importance of clockwise rotation and its value in differential diagnosis, and this point is also stressed by Goldberger (1953).

We have assumed the heart to lie in a vertical position when lead VL shows a QS or rS pattern, and in a horizontal position when VL shows a qR or QR pattern (Goldberger, 1953).

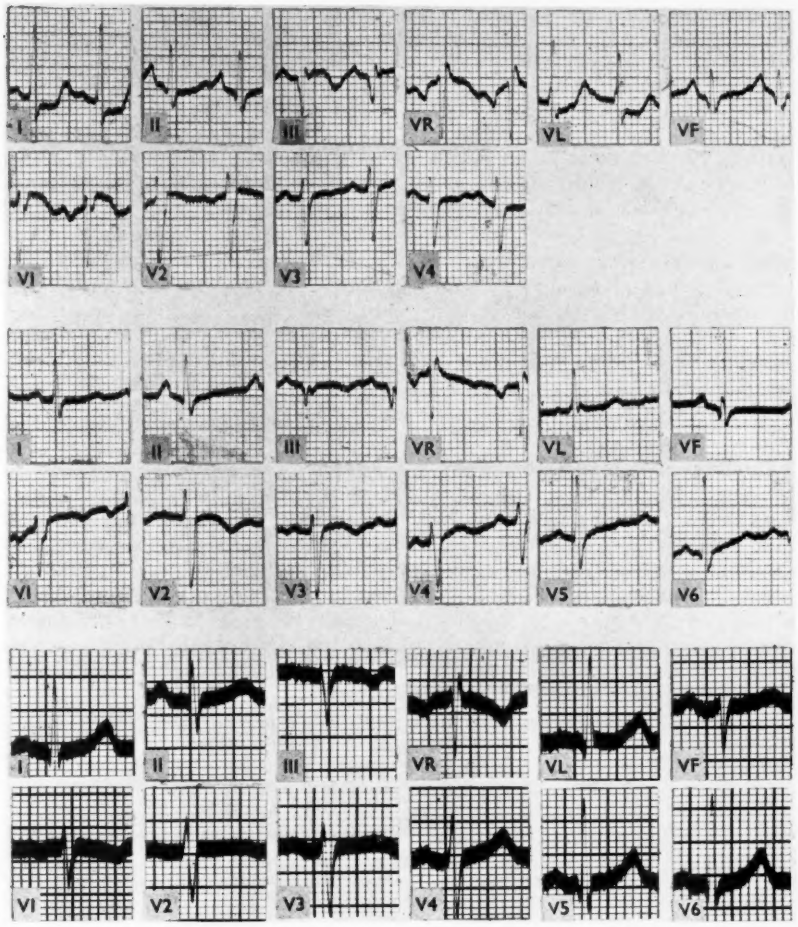


FIG. 1.—Case 35. 7/10/55: Tachycardia (rate 150). Clockwise rotation, S–T segment depression over the left ventricle, an S1 Q3 T3 pattern, right ventricular T wave inversion, and prominent P waves. 10/10/55: Disappearance of the S–T segment depression, but more obvious right ventricular T wave inversion. 24/11/55: Disappearance of the S1 and the Q3, reversion of the T waves towards normal, a more horizontal position of the heart, and disappearance of the prominent P waves. The T wave in lead III remains inverted.

Of the 50 patients, 33 showed electrocardiographic evidence that the heart was in a vertical position. Consideration of the two groups, severe and non-severe, showed that of the 28 severe cases 23 had hearts in a vertical position: of the 5 patients in this group who did not show this phenomenon, three were suffering from hypertension. In the 22 patients who comprised the non-severe group, 10 had hearts in a vertical position: of the 12 patients in this group in whom the heart was not vertical, four were suffering from hypertension and one from aortic valve disease.

Duration. Serial electrocardiograms were taken in 18 of the patients with vertical hearts and thus the duration of the vertical position could be ascertained. In five of these the electrical axis

changed towards the horizontal position as the effects of the embolism wore off. These changes took place in times varying from 5 to 56 days with an average of 33 days (see Fig. 1). In the other 13 patients, the heart remained in a vertical position for an average of 34 days, the range being from 2 to 120 days.

Clockwise rotation of the heart was diagnosed when the transitional zone, as shown by a complex in which the height of the R wave was equal to the depth of S, was shifted to the left of the V4 position. It was also diagnosed if a QR, Qr, or qR complex was present to lead VR (Goldberger, 1949). Of the 50 patients 30 showed clockwise rotation; of these 20 were severe cases: 22 patients showed a vertical axis combined with clockwise rotation and of these 16 were severe and 6 non-severe.

Serial electrocardiograms were taken of 15 patients with clockwise rotation. In four of these the rotation disappeared, and in five others the rotation became less, in periods varying from 2 to 120 days with an average of 29 days.

(iii) *Abnormalities of S1 Q3 T3*; (iv) *of S1 T3*; *and* (v) *of T3*. S1 Q3 T3 changes constitute the classic appearances first described by McGinn and White (1935) but they occurred in only 14 of our patients (see Fig. 1, 2, and 4). Eleven of these were severe and three were not so. In four others the cardiogram showed a conspicuous S wave in lead I and an inverted T wave in lead III, but no Q wave in this lead; three of these were severe. Nine patients, seven of them severe, showed an inverted T wave in lead III as the only significant finding in the standard leads.

It will be seen, therefore, that inversion of the T wave in lead III is a frequent finding in cases of pulmonary embolism, and a total of 27 patients showed this change, 21 of them being from the severe group. The exact cause of inversion of the T wave in lead III is difficult to determine. In many cases it is probably a positional phenomenon and in this series, all but 5 of the 27 patients with an inverted T wave in lead III, showed electrocardiographic evidence of a vertical position of the heart together with clockwise rotation. An inverted T wave in lead III, when present as an isolated finding, can have little diagnostic significance, but when combined with other changes it becomes of considerable importance. The relationship of these changes to those found in lead VF is discussed below.

Duration. The first of the S1 Q3 T3 changes to disappear was the deep S wave in lead I. Serial records were taken in 14 patients with this pattern. In 9 of these the S1 had disappeared or become considerably smaller in periods varying from 5 to 42 days with an average of 17 days (see Fig. 1 and 2). In the remaining five cases the follow-up period was not long enough to enable any change to be demonstrated.

The Q wave in lead III is the next of the changes in the standard leads to revert to normal. In 12 patients who had serial records taken, the Q waves disappeared or became considerably smaller in six, in periods varying from 2 to 48 days with an average of 21 days. In the remaining six the Q waves persisted, in one for as long as 68 days.

Of all the changes occurring in the standard leads in pulmonary embolism inversion of the T wave in lead III may be the most persistent. In 17 patients showing this feature of whom serial electrocardiograms were taken, the T wave became upright in three of them after 6, 8, and 16 days, but in the remaining 14 patients the T wave in lead III was still negative after an average of 38 days.

(vi) *Q waves in VF.* Although it has been stated that the absence of a Q wave in lead VF is of help in differentiating the electrocardiogram of pulmonary embolism from that of posterior cardiac infarction, Phillips and Levine (1950) have drawn particular attention to the appearance of a Q wave in lead VF after pulmonary embolism. We had only one example in which a Q wave of pathological dimensions occurred (Case 16, see Fig. 2) and in this patient it was present at 36 hours and was deeper eight days later. But in a further nine cases a small Q wave was discernible in lead VF, making a total of 10, six of which were from the severe group.

Duration. In eight cases in which a Q wave was present in lead VF and serial electrocardiograms were taken, it disappeared in three of them after 2, 15, and 27 days. This change seemed to

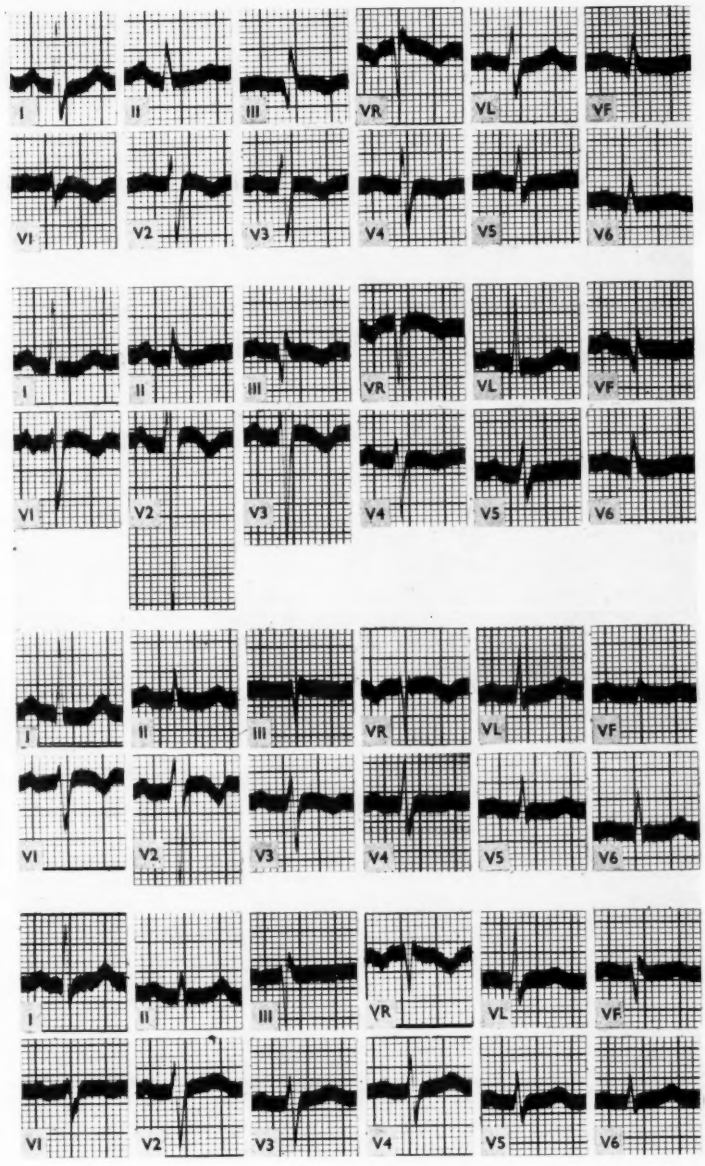


FIG. 2.—Case 16. 8/9/55: An S1 Q3 T3 pattern. A small Q wave and an inverted T wave in lead VF. Right ventricular T wave inversion. 15/9/55: The S wave in leads I and VL has disappeared. The Q wave in lead VF is more prominent and 0·04 sec. wide. 5/10/55: The Q3 has disappeared. The T waves are now positive in VF and also in V4. 4/11/55: The curves are now normal, only the flat T wave in lead III remains.

be associated with the heart taking up a more horizontal position. In the remaining five, one of which was followed up for 69 days, the Q waves persisted unaltered.

(vii) *T wave in VF.* Changes in the T wave in lead VF occurred in 23 patients. In 15 of these the T wave was negative, and in 8 of them it was flat. Seventeen of the 23 cases were in the severe group. All those with a negative T wave in lead VF also showed a negative T wave in lead III. However, in four instances the T wave in lead III was negative while that in lead VF was positive in the initial cardiograms.

Duration. Surprisingly, and in contrast to the persistence of the inversion of the T wave in lead III, the inverted T wave in lead VF was one of the first signs to disappear. Of 15 patients who had serial electrocardiograms and showed alteration of the T wave in lead VF, 13 showed that the T wave had become positive in an average of 15 days (see Fig. 2 and 3). In the remaining two the T wave changes persisted for 18 and 24 days respectively.

(viii) *S–T Segment Depression.* Depression of the S–T segment in leads I and II was mentioned as a significant finding in the original paper of McGinn and White (1935). Other authors, among them Murnaghan *et al.* (1943), Zuckerman *et al.* (1950), and Laham and Gerbaux (1951) have since pointed out that the S–T segment depression can also appear in lead VL and in those præcordial leads which face the left ventricle. Elevation of the S–T segment sometimes occurs in lead VR and, to a slight extent, in those præcordial leads that face the right ventricle.

In our series, S–T segment depression was seen best in leads I, II, and VL, while S–T elevation was most noticeable in lead VR. We found elevation of the S–T segment in præcordial leads over the right ventricle to be unusual, and it was never of such a degree as to resemble the appearance of an injury current.

Nine of our patients, eight of whom were from the severe group, had electrocardiograms showing S–T segment depression over the left ventricle (Fig. 1 and 4). However, one of them (Case 48) was a man of 74 with a blood pressure of 230/120 mm. Hg, and the depression of the S–T segment persisted unchanged for 13 days until his death; we think this depression was due to the effects of hypertension rather than to the pulmonary embolus. In the other eight cases the depression of the S–T segment in left ventricular leads was an early finding (Table III).

Duration. Four of the nine patients died and therefore in these the duration of the depression of the S–T segment could not be ascertained. In the remaining five the S–T segment depression quickly disappeared, with an average duration of 9 days.

TABLE III

SHOWING TIME OF ONSET AND DISAPPEARANCE OF S–T SEGMENT DEPRESSION

Case No.	Time between embolism and EC.	Leads showing S–T depression	Staircase ascent	Follow-up
45	1 hour	I, II, VL	Nil	Died
32	6 hours	I, II, VL	Present	S–T depression gone in 19 days
18	6 hours	I, II	Present	S–T depression gone in 2 days
35	8 hours	I, II, VL	Nil	S–T depression gone in 3 days
41	8 hours	I, II, VL, V3–V6	Present	Died
12	2 days	I, II, VL, V4–V6	Present	S–T depression gone in 14 days
43	2 days	I, II, VL	Nil	Died
28	3 days	I, II, VL	Nil	S–T depression gone in 7 days
48	13 days	I, II, VL, VF, V4–V6	Nil	Died

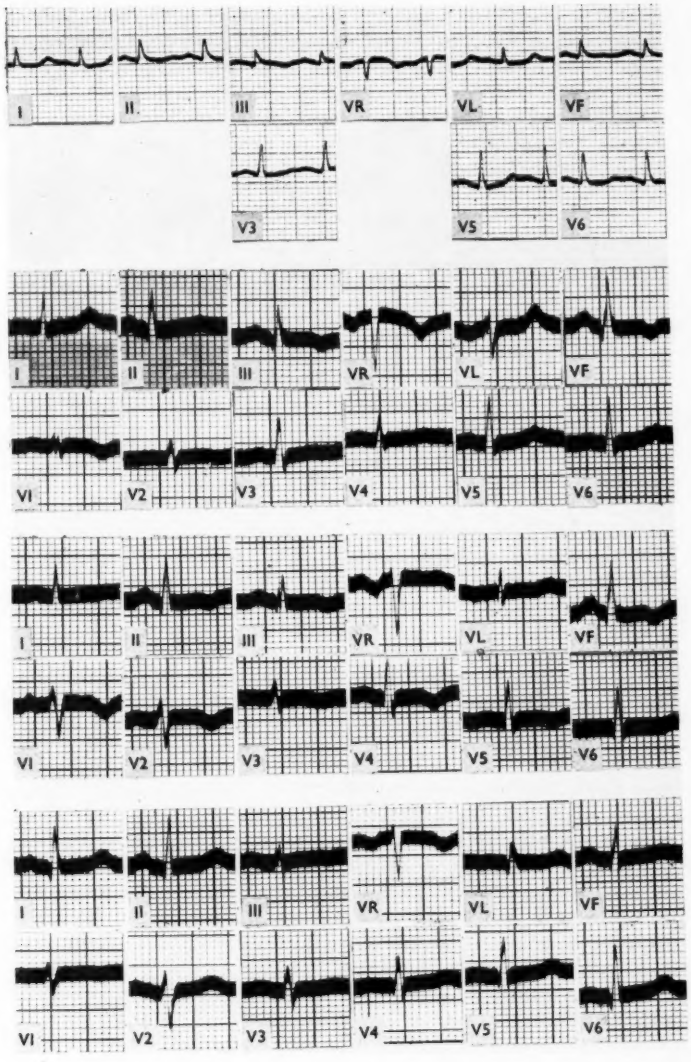


FIG. 3.—Case 38. 27/7/54: Tachycardia, a Q3 T3 pattern and a flat T wave in VF. 28/7/54: A vertical heart, an S1 Q3 T3 pattern, a small Q wave and an inverted T wave in VF, and flat T waves in the right præcordial leads. 29/7/54: Inverted T waves in leads II, III, VF, and V1–V6. 2/9/54: Reversion of the above changes towards normal.

It is likely that S–T segment depression may be more frequent than our figures suggest since it appears to be an early and transient finding. The gradual " staircase ascent " of the depressed S–T segment in leads I and II described by McGinn and White (1935) does not seem to us to be a very helpful sign, and to decide whether a particular electrocardiogram shows this sign or not is both difficult and unrewarding. Only four of our patients showed this pattern in an easily recognized form (Fig. 4).

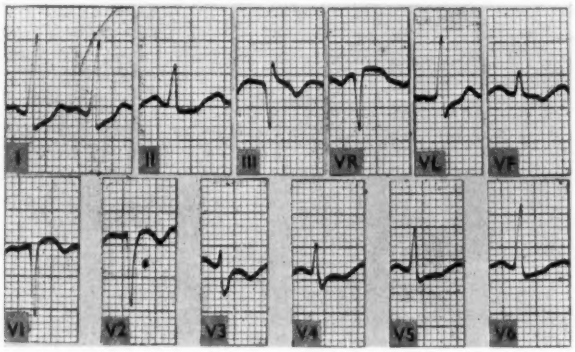


FIG. 4.—Case 41. Showing the " staircase " ascent of the S–T segment, particularly in lead I, also in leads VL, V5, and V6. Also an S1 Q3 T3 pattern, a negative T wave in VF, and right ventricular T wave inversion.

(ix) *Right Ventricular T wave Inversion.* Wood (1941) described 10 cases of pulmonary embolism in which leads IVR and bipolar leads from the left chest and right arm and the right chest and right arm were examined. He found that sharp inversion of the T wave occurred without appreciable displacement of the S–T segment. It has since been clearly established by Wood (1948), Myers *et al.* (1948), Phillips and Levine (1950), Laham and Gerbaux (1951), White (1951), Eliaser and Giansiracusa (1952), and Newman (1952) that in pulmonary embolism the T wave may be inverted in those præcordial leads that face the right ventricle.

In analysing our electrocardiographic findings we have disregarded T wave inversion in lead V1 because it is so frequently a normal finding; it may be of significance, however, in those cases in which a record of V1 taken before the embolism is available for comparison.

Of our 50 patients, 23 showed the T wave to be inverted in those præcordial leads that face the right ventricle (Fig. 1, 2, 3, and 4). Of these 23 cases 19 were severe. It was observed in four patients that the T wave inversion present in the electrocardiogram taken 24 hours after the embolism was deeper and more extensive two or three days later, though no fresh embolism had occurred (see Fig. 1 and 3). We have found that the T wave inversion seen in cases of pulmonary embolism may affect leads V1 and V2 only or may spread across the whole præcordial range, well beyond the transitional point, but that the T wave becomes less deeply inverted as the electrode is moved round towards the V6 position.

Duration. Serial electrocardiograms were taken of 13 patients with right ventricular T wave inversion. In eight of these the T wave changes gradually disappeared, starting first in the region of V5 and V6 and spreading towards V1 (Fig. 1, 2, and 3). The time taken for the abnormalities to disappear varied from 16 to 120 days with an average of 41 days. Of the remaining five patients, reversion of the T wave towards normal had started in three of them by the 10th, 24th, and 42nd day though it was not complete. The remaining two patients were followed only for 16 and 18 days and no changes in the T wave took place during this time.

(x) *Right Bundle-Branch Block.* Durant *et al.* (1939) published an account of three cases in which right bundle-branch block was seen to be present during the first hour or two after the embolism and disappeared after about 12 hours. Wood (1948) found transient right bundle-branch block patterns in three of his twenty cases.

Seven of our patients showed right bundle-branch block. It is noteworthy that these seven were not only classed as severe from the clinical point of view but that all of them died. Further details of these are shown in Table I (Cases 40, 42, 43, 45, 46, 49, and 50). The electrocardiograms of these patients had all been taken less than two days after the embolism, with the exception of Case 50 where the interval was 21 days. In Case 42 the patient was suffering from chronic cor pulmonale and could possibly have had the bundle-branch block before the embolism took place, but we have no evidence on this point. In Case 43 we know that bundle-branch block was not present in a cardiogram taken five months before the embolism occurred.

Duration. Serial electrocardiograms were obtained in only one patient of this group (Case 43) and in that instance they gave no information about the duration of the bundle-branch block because the changes only became obvious in the second one. The time intervals between the occurrence of the embolism and the taking of the electrocardiogram in our seven cases are as follows: Case 45, 1 hour; Cases 40 and 46, 12 hours; Cases 43 and 49, 24 hours; Case 42, 2 days; and Case 50, 22 days. Durant *et al.* (1939) were of the opinion that right bundle-branch block changes were an early finding and a transient one, but Case 50 in our series showed right bundle-branch block to be present 22 days after the embolism.

(xi) *Alteration in Cardiac Rhythm.* Murnaghan *et al.* (1943) found auricular fibrillation in four and auricular flutter in two out of a total of 92 examples of pulmonary embolism. Fliaser and Giansiracusa (1952) found auricular arrhythmia as a delayed phenomenon in three out of eight cases. Zuckerman *et al.* (1950) have described the production of auricular arrhythmias and A-V block of various degrees in experiments on dogs. On the other hand Newman (1952) is of the opinion that the sudden onset of sinus rhythm in a patient previously fibrillating is a sign suggesting pulmonary embolism, but we have not encountered such a case.

Seven of our 50 patients showed abnormalities of cardiac rhythm and six different types of rhythm were found.

Case 5 (non-severe) was a man of 68 years with hypertension (blood pressure 170/120 mm. Hg). Five days after the embolism the electrocardiogram showed partial heart block with a P–R interval of 0·24 sec. In Case 9 (non-severe) auricular fibrillation was present 24 hours after the embolism. Two days later another electrocardiogram showed sinus rhythm; a negative T3 and a flat TVF were the only remaining signs suggestive of pulmonary embolism. Case 11 (non-severe) showed auricular premature contractions three days after the embolism, but there was no other electrocardiographic abnormality. Case 15 (non-severe) showed auricular fibrillation two days after the embolism; two days later sinus rhythm was present and there were no other signs of pulmonary embolism on the electrocardiogram. Case 17 (severe) showed auricular flutter with an irregular ventricular response; the rhythm changed to auricular fibrillation at 12 days, back to auricular flutter at 15 days, to fibrillation once more at 21 days, and finally reverted to sinus rhythm 26 days after the embolism: the only other electrocardiographic signs of pulmonary embolism were a tiny Q wave in VF together with a flat T wave in that lead and in lead III. Case 29 (severe) 12 hours after the embolism showed multiple ventricular extrasystoles which had disappeared ten days later. Case 46 (severe) showed right bundle-branch block 12 hours after the embolism: the rate was 85 a minute except in lead V3 where a short bout of rapid beating was recorded, and auricular activity was not discernible in the præcordial leads so the mechanism of the arrhythmia was not obvious. This patient died three days after the embolism.

(xii) *Abnormalities of the P Wave.* It is considered unusual to find any alteration of the P wave in pulmonary embolism. Wood (1948) found it occasionally in massive pulmonary embolism and Zuckerman *et al.* (1950) mention right auricular dilatation as a late finding in experimental animals but they had no example in their clinical cases. Laham and Gerbaux (1951) found no P wave

abnormalities in 57 cases of pulmonary embolism. However, Eliaser and Giansiracusa (1952) found " P pulmonale " as a late manifestation in three out of eight cases.

Seven of our 50 patients showed abnormal P waves but one of these (Case 7) was suffering from mitral stenosis and had the typical wide bifid P waves associated with this condition, leaving six who showed alteration of the P pulmonale type for which no reason other than pulmonary embolism could be found. The typical appearance was seen best in lead II in five of the six cases and four out of the six were severe (Cases 33, 35, 43, and 47).

Case 5 has been mentioned above in the section on alterations of rhythm. In addition to partial heart block and S–T segment depression the electrocardiogram showed tall and spiked P waves, particularly in lead II. The record was taken five days after a pulmonary embolism.

A record taken nine days after the embolism in Case 22 showed an S1 T3 pattern, a negative T wave in lead VF, and right ventricular T wave inversion: the P waves were tall and spiked in leads II, III, and VF. A second cardiogram was not taken until 120 days later: this showed the P waves to be normal, a negative T wave in lead III being the only remaining abnormality.

Case 33 gave a history suggesting two pulmonary emboli at an interval of one week. In the record taken one day after the second embolism the spiked P waves were seen best in lead II, and Q3 T3 and TVF changes were present. The next record taken 33 days later no longer showed any P wave abnormality.

The electrocardiogram in Case 35 was taken eight hours after the pulmonary embolism: in addition to S1 Q3 T3 changes, S–T segment depression and right ventricular T wave inversion, the P waves were seen to be tall and spiked in leads II and VF. A second record taken three days after the embolism showed no change in this feature but the electrocardiogram taken 47 days after the embolism showed the P waves had returned to normal (Fig. 1).

In Case 43 a tracing taken two days after the embolism showed no abnormality of the P waves, but a record taken the next day showed them to be typically tall and spiked and seen best in leads V1 and V2. At autopsy multiple pulmonary emboli were present together with myocardial infarction.

In Case 47 the electrocardiogram taken three days after the embolism showed tall spiked P waves, best seen in lead II; an S1 T3 pattern with right ventricular T wave inversion was also present. The patient died ten days after the embolism and multiple emboli were found at necropsy.

Patients showing No Electrocardiographic Evidence of Pulmonary Embolism

In our series of 50 cases only 12 had electrocardiograms that showed nothing diagnostic or even suggestive of pulmonary embolism. The remaining 38 all showed electrocardiographic evidence which confirmed the diagnosis. Murnaghan *et al.* (1943) give figures indicating that about half their cases showed no electrocardiographic evidence of the diagnosis. Carlotti *et al.* (1947) found no electrocardiographic evidence of acute cor pulmonale in four-fifths of the cases so examined. Laham and Gerbaux (1951) found no suggestive electrocardiographic changes in 58 per cent of 57 cases.

A comparison of the severe and non-severe groups revealed that only one patient of the 28 in the severe group failed to show electrocardiographic evidence of pulmonary embolism, while on the other hand, 11 out of the 22 in the non-severe group showed no such signs.

The one severe example (Case 31) showing no evidence of pulmonary embolism was a woman of 59 years who had undergone a Wertheim hysterectomy 14 days before the embolism took place. She collapsed whilst at stool and was found to be distressed, dyspnœic, and cyanosed. Thrombosis of the right saphenous vein was discovered, and a little later a pleural rub developed at the base of the right lung. An X-ray of the chest taken the next day showed the appearance of a recent pulmonary infarct in the right lower lobe. The electrocardiogram taken the same day (Fig. 5) showed poor voltage curves but the tracing was not diagnostic or even suggestive of pulmonary embolism.

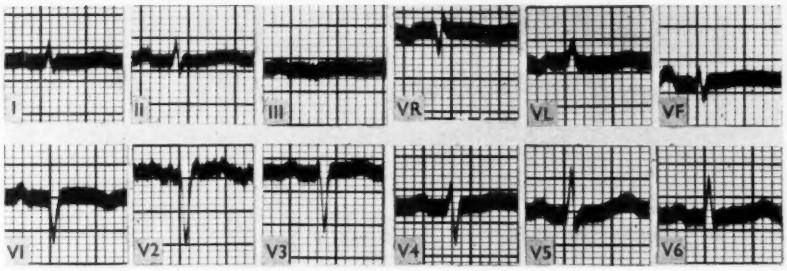


FIG. 5.—Case 31. From a severe case of pulmonary embolism. This tracing was taken two days after the embolism (see text).

PULMONARY EMBOLISM ASSOCIATED WITH MYOCARDIAL INFARCTION

Phillips and Levine (1950) describe a patient (their Case 6) with evidence of old posterior myocardial infarction, who suffered a pulmonary embolism and whose electrocardiogram showed evidence of both conditions. Newman (1952) mentions five cases in which antecedent myocardial infarction distorted the electrocardiographic pattern of pulmonary embolism and made it unrecognizable. Goldberger (1953) states that if pulmonary embolism occurs after myocardial infarction the tracing continues to show only the pattern of the myocardial infarct. In view of the difficulty sometimes encountered at the bedside in differentiating cardiac infarction from pulmonary embolism, the electrocardiographic appearances when both lesions are present are of more than academic importance. In one of our cases, with autopsy confirmation, the cardiographic evidence of the myocardial infarct was completely masked by that of pulmonary embolism and we believe this to be an unusual finding.

A man of 66 (Case 43) was admitted to hospital in 1952 because of anterior myocardial infarction, from which he made a good recovery (Fig. 6, record of 9/3/52). In 1954, during the course of one week he became increasingly short of breath, had a number of hæmoptyses, and was admitted to hospital again. A few hours after his admission he collapsed and became comatose with a pulse rate of 120 a minute, a raised venous pressure, triple rhythm, and diminished breath sounds over the left lower lobe.

On 4/7/54, two days after admission to hospital, the standard leads only were recorded at 11.30 a.m. These tracings showed an auricular rate of 200 a minute with a variable ventricular response of about 150 a minute; there was also an S1 Q3 appearance with some elevation of the S–T segment in lead III. The standard leads were recorded again at 9.30 p.m. on the same day and these tracings showed sinus rhythm at a rate of 100 a minute; the elevation of the S–T segment in lead III was no longer obvious and an S1 Q3 T3 pattern had developed. On the following day a 12-lead electrocardiogram was taken and in this tracing the S1 Q3 T3 pattern had disappeared, the P waves were tall and bifid in leads I, V1, and V2, and partial right bundle-branch block was visible in leads V1 and V2; all the T waves were of poor voltage except those in VL which were negative. He died the following day and autopsy showed multiple recent infarcts in the left lower lobe and also in the right lung. There was also evidence of both old and recent myocardial infarction in the lower part of the anterior wall and the apex of the left ventricle.

Comment. The S1 Q3 T3 appearance in the standard leads on 4/7/54 was considered virtually diagnostic of pulmonary embolism. In the record of 5/7/54 the standard leads looked entirely different and apart from the sudden alteration of the shape of the P wave they did not suggest pulmonary embolism; in leads V1 and V2, however, the presence of a partial right bundle-branch block pattern with a QRS interval of 0·12 sec. supported this diagnosis. There was no electrocardiographic evidence of recent or old myocardial infarction but the flat or negative T waves over the left ventricle suggested that the myocardium in this situation was not normal.

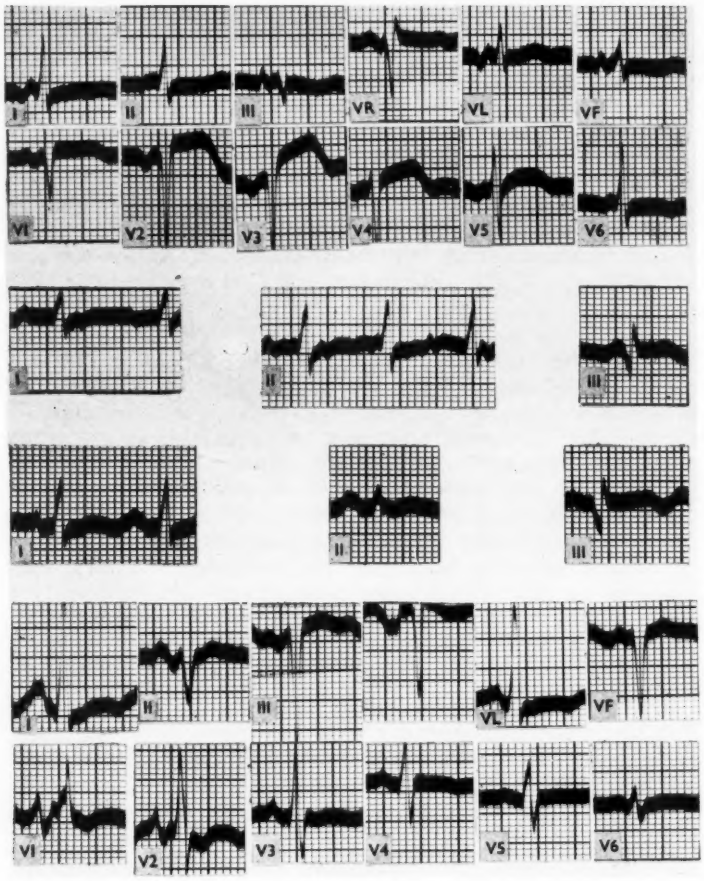


FIG. 6.—Case 43. Pulmonary embolism with myocardial infarction. 9/3/52: The original myocardial infarct. 4/7/54, 11.30 a.m. Auricular tachycardia with an irregular ventricular response. There is also an S1 Q3 pattern. 4/7/54, 9.30 p.m. Sinus rhythm and an S1 Q3 T3 pattern. 5/7/54: Partial right bundle-branch block. Inverted T waves in leads I and VL, flat T waves over the left ventricle.

The electrocardiographic findings in this patient seem to be different from those of previously reported cases, in that evidence of pulmonary embolism is seen whereas that of myocardial infarction is not.

DISCUSSION

As a result of pulmonary embolism, alteration in the electrocardiogram may occur in the standard leads, the unipolar limb leads, or the chest leads. These changes do not necessarily appear in all leads, nor do they necessarily occur simultaneously. In a suspected case it is important, therefore, always to take a 12-lead electrocardiogram and to repeat the record later if doubt still exists. We would emphasize the value of serial records in difficult cases. In some of our more recent patients

we recorded leads V3R and V4R to see if they gave any further information, but so far we have not found these leads to be of great value except that sometimes they gave a clearer indication of right bundle-branch block.

Common Diagnostic Patterns. The 12 electrocardiographic changes that we have described may occur separately or combined together in various ways. When they occur alone they may be of little help in diagnosis, but when one compares the various combinations of abnormal patterns with the clinical and autopsy findings, eight recognizable different appearances can be distinguished. We have arranged these patterns in order of their diagnostic reliability (Table IV), and the first three we consider to be diagnostic of pulmonary embolism.

TABLE IV

THE EIGHT ELECTROCARDIOGRAPHIC PATTERNS COMMONLY FOUND IN PULMONARY EMBOLISM, IN ORDER OF DIAGNOSTIC RELIABILITY *

Pattern in electrocardiogram	Number of cases	Number that were severe	Number of deaths
1. S1 Q3 T3 plus right ventricular T wave inversion	9	7	2
2. S1 T3 or T3 plus right ventricular T wave inversion	9	8	1
3. S1 Q3 T3 plus right bundle-branch block	3	3	3
4. Right ventricular T wave inversion alone	3	2	0
5. S1 Q3 T3 alone	2	2	0
6. Right bundle-branch block alone	4	4	4
7. S1 T3 or T3 with or without T changes in VF	4	2	1
8. Sinus tachycardia, vertical heart, clockwise rotation alone	1	1	0

* To any of the above patterns may be added P pulmonale, depression of the S–T segment in leads over the left ventricle, and various arrhythmias (see text).

Patterns Typical of Pulmonary Embolism

1. *S1 Q3 T3 plus Right Ventricular T wave Inversion.* This pattern was the most common and also the most reliable indication of pulmonary embolism (Fig. 1, 2, 3, and 4). To the best of our knowledge such a pattern does not occur in any other condition. It was seen in nine cases, seven of which were severe.

2. *S1 T3, or T3 Changes, plus Right Ventricular T Wave Inversion.* This pattern was equally common, and taken in conjunction with the clinical picture is virtually diagnostic. It occurred in nine cases, eight of which were severe.

3. *S1 Q3 T3 plus Right Bundle-Branch Block.* Three of the patients with right bundle-branch block also showed an S1 Q3 T3 appearance, all of them were severe cases and died. This combination we also consider to be diagnostic of pulmonary embolism.

Patterns Suggestive of Pulmonary Embolism

1. *Right Ventricular T wave Inversion Alone.* This pattern occurred in three cases, two of which were severe. Although the change is not in itself a specific one, we have found it of help in diagnosis since the other conditions giving rise to it are not likely to be confused with pulmonary embolism with the possible exception of antero-septal cardiac infarction. The differences in that condition are discussed below in the section on differential diagnosis.

2. *S1 Q3 T3 Pattern Alone.* Although this well-known pattern may indicate pulmonary embolism it is not so reliable a diagnostic sign as any of the previous four patterns. It occurred in two patients, both severely ill. At times, posterior cardiac infarction may be accompanied by a deep S wave in lead I, although this is uncommon, but when such a wave is present the appearance may be indistinguishable from that due to pulmonary embolism.

3. *Right Bundle-Branch Block Alone.* The diagnostic value of this pattern is difficult to assess.

Right bundle-branch block unaccompanied by any other electrocardiographic evidence of pulmonary embolism was present in four of our cases, all of which were severe. It may occur, of course, in other conditions that give rise to strain on the right ventricle, and for this reason records showing this pattern should be interpreted only in relation to the history and physical signs. Serial tracings may help because other electrocardiographic signs more typical of pulmonary embolism are apt to appear in subsequent records.

4. *S1 T3 or T3 Changes Alone.* Although this pattern occurs in pulmonary embolism (four cases) it may so frequently be present for other reasons that it cannot be considered of much confirmatory value. Simultaneous inversion of the T wave in lead VF is common to this pattern.

5. *Sinus Tachycardia, Clockwise Rotation, Vertical Heart.* This pattern was frequent and all three features occurred in 22 of 50 patients, but it was usually combined with other changes, and as an isolated finding occurred in only one patient. By itself it is often a normal finding, but there is one occasion on which it is of help as a diagnostic sign, namely when it appears suddenly in a patient whose previous electrocardiogram showed a different pattern.

To any of the above patterns may be added the typical tall, spiked P pulmonale, usually best seen in standard lead II, but as mentioned previously this abnormal P wave is often of very short duration and was present in the records of only 6 of 50 patients. Nevertheless, when present it greatly strengthens the diagnosis, particularly if it is a transient finding. Similarly, depression of the S–T segment in leads over the left ventricle may accompany any of the above patterns, and in eight out of nine of the patients showing this sign the illness was severe.

Although alteration of rhythm occurred in seven patients, the various arrhythmias produced are not characteristic of pulmonary embolism.

Differential Diagnosis

As we have shown, some of the electrocardiographic patterns seen in pulmonary embolism are diagnostic, but some are difficult to distinguish from those seen in other conditions. It should be emphasized that the diagnosis is primarily a clinical matter and that the electrocardiogram should be looked upon as an aid to the history and physical signs. Unlike the high degree of accuracy shown by electrocardiography in the diagnosis of myocardial infarction, in pulmonary embolism one can expect equivocal findings more often than not. Even so, it is our opinion that more assistance can be obtained from electrocardiography in the diagnosis of pulmonary embolism than is currently believed.

The electrocardiogram in chronic cor pulmonale is possibly the most likely to simulate that of pulmonary embolism. It may show right ventricular T wave inversion and an S1 T3 pattern together with a vertical heart and clockwise rotation. On clinical grounds, however, it is usually easy to distinguish this type of case from pulmonary embolism, but the occurrence of pleuritic pain and hæmoptysis in a patient with chronic bronchitis and emphysema may present a difficult problem, and for that matter such patients, if bedridden, may suffer embolic pulmonary infarction. There are two electrocardiographic points of difference between chronic cor pulmonale and pulmonary embolism. The first is that many cases of pulmonary heart disease show a tall spiked P wave as a permanent feature in the electrocardiogram. Wood (1948) found this in 85 per cent of 100 cases. On the other hand, the finding of these abnormal P waves is rare (6 out of 50 of our cases) and also of much shorter duration in pulmonary embolism. The second is the concomitant finding of right ventricular hypertrophy in chronic cor pulmonale; this is not seen in uncomplicated pulmonary embolism.

Antero-septal myocardial infarction is sometimes diagnosed in error when in fact pulmonary embolism is present. In our view this difficulty has not been sufficiently emphasized. In antero-septal infarction the presence in the præcordial leads of an injury current or of abnormal Q waves will clarify the diagnosis in the majority of cases because neither of these signs occurs in pulmonary embolism. In pulmonary embolism the T wave inversion is usually deepest in leads V1 and V2, becoming progressively less towards V6, whereas gradual lessening of the inversion of the T wave

from leads V1 to V5 is not necessarily a feature of anteroseptal infarction. The S1 Q3 T3 pattern found in pulmonary embolism is not a feature of anteroseptal infarction, though clockwise rotation may occur in the latter condition. Serial electrocardiograms will show the two maladies to progress in different ways.

In differentiating posterior myocardial infarction from pulmonary embolism the significance of a Q wave in association with an inverted T wave in leads III and VF has been the subject of considerable discussion. Phillips and Levine (1950) illustrated these difficulties with one of their cases and Newman (1952) drew up a list of differences between the electrocardiographic findings in pulmonary embolism and posterior myocardial infarction. In our series we have not encountered much difficulty, and although ten cases showed a Q wave in lead VF, in only one was it of pathological dimensions (Case 16, see Fig. 2). Phillips and Levine (1950) found a conspicuous Q in VF in two of their eight cases. Their cardiograms were taken a few hours after the embolism whereas some of ours were taken considerably later (Table V). If the heart is in a vertical position and clockwise rotation together with forward rotation of the apex is present, we do not think that the appearance of even a deep Q wave in lead VF is unexpected in pulmonary embolism. In such instances the QR and downward T in lead VF will be accompanied by an RS in lead VL and a QR in lead VR.

TABLE V

TIME INTERVAL BETWEEN THE EMBOLISM AND FIRST ELECTROCARDIOGRAM AND THE NUMBER OF CASES WITH POSITIVE OR NEGATIVE ELECTROCARDIOGRAPHIC FINDINGS

Time between embolism and first EC.	No. of cases with positive findings	No. of cases with negative findings
12 hours or less	7	0
24 hours	7	2
2 days	7	1
3 days	4	3
4 days	1	0
5 days	4	2
6 days	3	0
7 days	0	1
More than 7 days	5	3

We find that the most important point in the diagnosis is the presence of an injury current in leads III and VF in many cases of posterior infarction, such an appearance never being found in pulmonary embolism. Also, in uncomplicated posterior infarction the T waves in the præcordial leads may be tall but they are never inverted, whereas in pulmonary embolism the præcordial T waves may be normal, flat or inverted, but not tall. Goldberger (1953) states that the clockwise rotation of the heart, common in pulmonary embolism, is unusual in posterior infarction unless anterior infarction is also present.

The right ventricular strain pattern from any cause shows T waves indistinguishable from those seen in pulmonary embolism. Transient changes can occur in rheumatic carditis, diphtheria, and pneumonia. Phillips and Levine (1950, their Case 7) described similar appearances due to massive collapse of the lungs, though the T wave inversion was only obvious in lead V1. In normal infants or children the T waves may be inverted in those præcordial leads that face the right ventricle (Zeigler, 1951). Pulmonary embolism occurring in a young child might well present a confusing electrocardiographic appearance, but we have not encountered such a case. Goldberger (1953) published tracings of a normal adult showing right ventricular T wave inversion with a " juvenile T wave pattern".

Comparison of Severe and Non-severe Groups

In the group of 28 patients that we have called severe, significant electrocardiographic findings were far more frequent than in the non-severe cases. No fewer than 27 of them showed evidence of pulmonary embolism in the electrocardiogram. In the same group there were 19 examples of right ventricular T wave inversion and 11 examples of the complete McGinn and White (1935) pattern. All seven examples of right bundle-branch block, either alone or accompanied by the S1 Q3 T3 appearance, were also from the severe group.

In the 22 patients belonging to the non-severe group the figures were very different. Only 11 showed any evidence of pulmonary embolism in the electrocardiogram. Among these eleven there were four examples of right ventricular T wave inversion and three of the complete McGinn and White pattern: there were no instances of bundle-branch block (Tables II and VI).

TABLE VI

A Comparison of the Findings in the Severe and Non-severe Groups

	Electro-cardiographic changes		RV T wave inversion		S1 Q3 T3 pattern		RBBB		Rhythm alterations	
	Positive	Negative	Present	Absent	Present	Absent	Present	Absent	Present	Absent
Severe	27	1	19	9	11	17	7	21	3	25
Non-severe ..	11	11	4	18	3	19	—	22	4	18

Of the 22 non-severe cases it was noteworthy that 18 had pleuritic pain followed by hæmoptysis. Such syndromes do not generally present diagnostic difficulties; this is fortunate because in our series electrocardiography yielded no information in one-half of them. It is in the clinically less obvious combinations of sudden dyspnœa, fall in blood pressure, or syncope that electrocardiography may be of considerable value. In them positive electrocardiographic evidence of pulmonary embolism was found in 27 of 28 cases (Table VI).

The Relationship of Pulmonary Infarction to the Electrocardiographic Findings

Little attention has been paid to the presence or absence of pulmonary infarction in relation to the electrocardiographic pattern in pulmonary embolism. Sokolow *et al.* (1940) and Laham and Gerbaux (1951) could not demonstrate any correlation. We have found that there is a rough relationship between the presence of pulmonary infarction and the electrocardiographic findings, but the inherent difficulties in deciding upon the presence or absence of pulmonary infarction makes accurate correlation difficult. Of our 11 patients coming to necropsy, five had pulmonary infarction and six did not. In the others we have relied on the X-ray findings described by Short (1951) to indicate pulmonary infarction. X-rays of the chest were taken after the pulmonary embolism in 34 patients and of these 25 showed evidence of pulmonary infarction. Thus of the 45 patients with embolism, 30 showed infarction and 15 did not.

The absence of infarction meant a more serious illness. Of the 15 patients without it 13 belonged to the severe group, whereas of the 30 who had pulmonary infarcts only 14 were severe (Table VII).

Electrocardiographic Correlation

In pulmonary embolism severe disturbance of the circulation with embarrassment of the right ventricular muscle is shown electrocardiographically by right ventricular T wave inversion and right bundle-branch block. In our series these patterns occurred more frequently in the absence of pulmonary infarction than in its presence (Table VII). Newman (1952) states that the severity and magnitude of the pulmonary infarction do not necessarily run parallel with the extent of the

TABLE VII

A Comparison between Patients with Pulmonary Infarction and those without

	Severity		RBBB		RV T wave inversion		Deaths	
	Severe	Non-severe	Present	Absent	Present	Absent	Survived	Died
Pulmonary infarction ..	14	16	3	27	11	19	25	5
No pulmonary infarction	13	2	4	11	8	7	9	6

electrocardiographic change and cannot be estimated from it. We agree that the size of the pulmonary infarct cannot be correlated with the electrocardiographic findings, but it is possible that there is a relationship between the size of the embolus and the presence or absence of infarction. It is recognized that large emboli often do not cause pulmonary infarction. It is possible, therefore, that many patients who show no infarction may have had a large embolism. This seems to be borne out by our experience. Thus in our series it is not the size of the infarct that determines cardiographic abnormalities but the grade of the circulatory effects of the embolism. The severity of the case, as defined by us, and the cardiographic changes run very largely parallel (Table VII).

Malinow *et al.* (1946) working with dogs, and Phillips and Levine (1950) produced evidence showing that small emboli could cause profound effects on the circulation, out of all proportion to their size. Two of our post-mortem examinations (Cases 46 and 50) revealed emboli in only one branch of the pulmonary artery, and in two others (Cases 40 and 44) the embolus was found in branches of the second order.

Animal experiments by Gibbon *et al.* (1932), however, indicate that more than 50 per cent of the pulmonary circulation must be occluded before a significant fall in systemic blood pressure occurs and this has been confirmed by Love *et al.* (1938). In man electrocardiograms were recorded during and after pneumonectomy by Barnes (1941) and Semisch and Merves (1942) because it was thought that the sudden occlusion of about one-half of the pulmonary circulation might be reflected in the tracings: Semisch and Merves found surprisingly little electrocardiographic evidence and Barnes found none.

The foregoing facts suggest that there is some process other than simple occlusion by the embolus involved in the production of acute cor pulmonale. The existence of a pulmonary vasoconstrictor reflex has been suggested by Megibow *et al.* (1942) and by Zuckerman *et al.* (1950) and this seems to be the most likely explanation, but the mechanism of the reflex has always been obscure. Recently Smith and Smith (1955) have postulated a humoral mechanism with " serotonin " (5 hydroxytryptamine) as the agent. According to Zucker (1953) this substance is released from platelets in the first stage of clot formation, and causes a sharp rise of pressure when it reaches the pulmonary circulation. This hypothesis would provide explanations for many of the apparent anomalies seen in pulmonary embolism. It might explain the very variable duration of some of the electrocardiographic findings and also why a normal electrocardiogram can be found two days after what appeared to be a very severe embolism, as in our Case 31.

Summary

Ninety-four patients diagnosed as suffering from pulmonary embolism were examined and in 50 of these the diagnosis was considered certain, either as a result of necropsy or by clinical and radiological criteria that we have defined.

Analysis of the electrocardiograms of these 50 patients showed 12 different signs; these are described and their frequency and duration recorded.

When the 12 electrocardiographic signs were considered together, they were seen to fall into

eight common patterns, the first three of which we consider to be diagnostic of pulmonary embolism, namely: S1 Q3 T3 appearance plus right ventricular T wave inversion,
S1 T3 or T3 appearance plus right ventricular T wave inversion, and
S1 Q3 T3 appearance plus right bundle-branch block.

The remaining five patterns are highly suggestive of the diagnosis when considered in relation to the clinical history.

There was no arrhythmia particularly characteristic of pulmonary embolism. The much quoted " staircase ascent " of the S–T segment was in our experience of little diagnostic value. A tall spiked P wave was found in six cases out of 50, four of which were severe.

The electrocardiographic findings have been correlated with the clinical severity of the cases, 28 of which were classed as severe and 22 as not severe. The findings in embolism with pulmonary infarction are compared with those in embolism without pulmonary infarction. The latter group showed electrocardiographic signs more frequently than the former.

The differential diagnosis is discussed.

Details are given of an example of pulmonary embolism occurring at the same time as myocardial infarction, the cardiograms showing signs of pulmonary embolism, but not of cardiac infarct.

It is our opinion that more assistance can be obtained from electrocardiography in the diagnosis of pulmonary embolism than is commonly believed. Of the 50 cases, 38 showed cardiographic evidence of pulmonary embolism and these signs sometimes persisted for more than two months. It is particularly in the clinically less obvious illnesses with dyspnœa, and fall in blood pressure or syncope that it can help, and 27 of 28 such cases showed electrocardiographic evidence of pulmonary embolism.

References

Barnes, A. R. (1937). *J. Amer. med. Ass.*, **109**, 1347.
Barnes, C. (1941). *Proc. roy. Soc. Med.*, **34**, 606.
Carlotti, J., Hardy, I. B., Linton, R. R., and White, P. D. (1947). *J. Amer. med. Ass.*, **134**, 1447.
Durant, T. M., Ginsberg, I. W., and Roesler, H. (1939). *Amer. Heart J.*, **17**, 423.
Eliaser, M., and Giansiracusa, F. (1952). *Amer. Heart J.*, **43**, 533.
Gibbon, J. H., Hopkinson, M., and Churchill, E. D. (1932). *J. clin. Invest.*, **11**, 543.
Goldberger, E. (1949). *Amer. J. Med.*, **7**, 756.
—— (1953). *Unipolar Lead Electrocardiography and Vectorcardiography*. 3rd ed. London.
Horn, H., Dack, S., and Friedberg, C. K. (1939). *Arch. intern. Med.*, **64**, 296.
Katz, L. N. (1946). *Electrocardiography*. 2nd ed. Philadelphia.
Kuo, P. T., and Vander Veer, J. B. (1950). *Amer. Heart J.*, **40**, 825.
Laham, J., and Gerbaux, A. (1951). *Arch. Mal. Cœur*, **44**, 328.
Love, W. S., Brugler, G. W., and Winslow, N. (1938). *Ann. intern. Med.*, **11**, 2109.
Malinow, M. R., Katz, L. N., and Kondo, B. (1946). *Amer. Heart J.*, **31**, 702.
McGinn, S., and White, P. D. (1935). *J. Amer. med. Ass.*, **104**, 1473.
Megibow, R. S., Katz, L. N., and Steinitz, F. S. (1942). *Surgery*, **11**, 19.
Murnaghan, D., McGinn, S., and White, P. D. (1943). *Amer. Heart J.*, **25**, 573.
Myers, G. B., Klein, H. A., and Stoffer, B. E. (1948). *Amer. Heart J.*, **35**, 1.
Newman, D. A. (1952). *J. Fla. med. Ass.*, **38**, 701.
Phillips, E., and Levine, H. D. (1950). *Amer. Heart J.*, **39**, 205.
Semisch, C. W., and Merves, L. (1942). *Arch. intern. Med.*, **69**, 417.
Short, D. S. (1951). *Quart. J. Med. N.S.*, **20**, 233.
Smith, G., and Smith, A. N. (1955). *Surg. Gynec. Obstet.*, **101**, 691.
Sokolow, M., Katz, L. N., and Muscovitz, A. N. (1940). *Amer. Heart J.*, **19**, 166.
White, P. D. (1935). *Ann. intern. Med.*, **9**, 115.
—— (1951). *Heart Disease*. 4th ed. New York.
Wilson, F. N., Rosenbaum, F. F., and Johnston, F. D. (1947). *Advanc. intern. Med.*, **2**, 1.
Wood, P. (1941). *Brit. Heart J.*, **3**, 21.
—— (1948). *Brit. Heart J.*, **10**, 87.
Zeigler, R. F. (1951). *Circulation (N.Y.)*, **3**, 438.
Zucker, M. B. (1953). *Abstracts of Communications: Nineteenth International Physiological Congress*, p. 915.
Zuckerman, R., Rodriguez, M. I., Sodi Pallares, D., and Bisteni, A. (1950). *Amer. Heart J.*, **40**, 805.

AUSCULTATION IN PATENT DUCTUS ARTERIOSUS

WITH A DESCRIPTION OF TWO FISTULÆ SIMULATING PATENT DUCTUS

BY

CATHERINE NEILL* AND PATRICK MOUNSEY

From the Cardiac Department of The London Hospital

Received May 23, 1957

The purpose of this paper is to describe the characteristics of the murmur of patent ductus, to show in what way auscultation may be modified by pulmonary hypertension, a large shunt, or associated heart disease, and to compare the continuous murmur of patent ductus with continuous murmurs due to other causes.

The Investigation Described

A series of 73 patients with patent ductus is described, of whom 71 were selected for surgical treatment, while the two remaining patients had complicating severe pulmonary hypertension with a right-to-left shunt. The diagnosis of patent ductus was confirmed at operation in 71 patients. In the two patients with pulmonary hypertension, who were not treated by operation, necropsy proof of the diagnosis was obtained.

In the nine-year period, during which these patients were operated upon, six other patients were submitted to thoracotomy, in whom the ductus was found to be closed. In four of these patients the diagnosis remains in doubt, although one patient is thought to have an aorto-pulmonary septal defect. The other two patients with fistulae have been further investigated and submitted to a second operation; in one it has been shown to be between the aorta and right ventricle and in the other between the coronary artery and right ventricle.

Clinical examination was amplified by a phonocardiogram in every patient and in 20 a post-operative phonocardiogram was obtained. Routine examination before operation also included a teleradiogram and an electrocardiogram. Cardiac catheterization was performed in 12 patients in whom pulmonary hypertension, a large shunt, or associated heart disease indicated the need for fuller investigation. Angiocardiography was carried out in one patient, in whom coarctation and an aneurysm of the aorta were present in addition to a patent ductus.

Clinical Features

There were 63 female and 10 male patients. The age at operation ranged from 18 months to 63 years. Seven were under 5 years, 36 between 5 and 15, 23 between 15 and 30, and five over 30 years. The patients with severe pulmonary hypertension, not operated upon, were 15 and 56 years old respectively when they died; both were female. Seventy-one of the patients were in sinus rhythm, but the two oldest, aged 49 and 63 years, were in atrial fibrillation.

Two inter-related variables influence the clinical picture of patent ductus namely the volume of the left-to-right shunt and the degree of complicating pulmonary hypertension, which may be present. Most patients have a small shunt and their pulmonary arterial pressure is not significantly raised. There were 49 such patients in the present series. These patients were free from symptoms, had a typical continuous murmur, a pulse that was normal or only slightly collapsing in character

* Now Assistant Professor of Pediatrics, Johns Hopkins University, Baltimore.

and a prominent pulmonary artery without much pulsation. In addition the signs of left ventricular enlargement were slight or absent both on screening and in the electrocardiogram, and at operation the ductus was found to be small, with an external diameter of less than 1 cm.

A *large shunt* was diagnosed in 22 patients in whom there was considerable left ventricular enlargement shown by a cardio-thoracic ratio of 60 per cent or more, left ventricular preponderance in the electrocardiogram, a large ductus with an external diameter of 1 cm. or more, and an unusually strong thrill at operation. In addition they had a wide pulse pressure, pulmonary plethora, obvious hilar dance, and in eight patients there was a functional mid-diastolic murmur. Cardiac catheterization was carried out in 6 of the 22 patients and indicated that the pulmonary flow was at least twice the systemic. Considerable variation may occur, however, in the oxygen content of samples from the pulmonary artery, withdrawn from different sites and at different phases in the cardiac cycle in patients with a patent ductus. This may be due to streaming of the blood entering simultaneously from the right ventricle and the ductus, and also to the fact that the pulmonary arterial blood is probably more saturated in diastole, when the ductus alone is feeding it, than in systole. These factors are likely to introduce a considerable margin of error into a detailed estimation of the volume of the shunt.

Whereas the presence of a large shunt does not make clinical diagnosis more difficult, *pulmonary hypertension* may profoundly modify the characteristic signs of patent ductus. Where the pulmonary arterial pressure, although raised, remains well below the systemic pressure, the clinical picture is little affected. A continuous murmur is audible, there is no right ventricular preponderance in the electrocardiogram, and the elevation of the pulmonary pressure is reversible by surgery, the increased pressure being directly related to the increased flow in these patients.

Where the pulmonary arterial pressure approaches that of the aorta, the characteristic continuous murmur of patent ductus is lacking. These patients, sometimes said to have " balanced ductus ", form a small, but important, group. They have the clinical signs of a large left-to-right shunt, including a wide pulse pressure, pulmonary plethora, and radiological evidence of left ventricular enlargement. The electrocardiogram shows dominant left ventricular preponderance with added signs of right preponderance. The diagnosis can be suspected on clinical grounds, but can only be established with certainty by passage of a cardiac catheter through the ductus or by retrograde aortography. These patients are greatly benefited by surgery, if the diagnosis is made early, before calcification of the ductus and pulmonary artery or other complications ensue. There were two such patients in the present series. In one, aged 33, cardiac catheterization showed a continuing left-to-right shunt through the ductus, although the diastolic pressure in the pulmonary artery and aorta were equal, the aortic pressure being 150/60 and the pulmonary arterial pressure being 115/60 mm. Hg. At operation the external diameter of the ductus was very large and there was more extensive calcification than had been apparent radiologically (Fig. 1), which extended into the aorta and pulmonary artery. It was decided that neither ligation nor division of the ductus could be safely performed. In the other patient, aged 26, who was in heart failure during pregnancy, there was aneurysmal enlargement of the pulmonary artery, which showed vigorous pulsation, and plethora, so that the radiological picture closely resembled that of atrial septal defect. The electrocardiogram, however, showed dominant left ventricular preponderance and the pulse was collapsing in character. Cardiac catheterization was cut short by a serious arrhythmia. At operation the ductus, which was found to be very large, with an external diameter of 2 cm., was satisfactorily divided, and since operation the patient has made an uninterrupted recovery.

Where the pulmonary arterial pressure exceeds that in the aorta and the direction of the shunt through the ductus is reversed, there is cyanosis best seen in the lower extremities, no continuous murmur, a loud pulmonary second sound, a large pulmonary artery, clear peripheral lung fields and right ventricular preponderance in the electrocardiogram. Operation is contra-indicated in these patients (Johnson *et al.*, 1950; Cosh, 1953; Dammann *et al.*, 1953). Two patients with this clinical picture were included in the present series. One had been cyanosed since the age of five and dyspnœic since the age of ten; she died when she was 15 years old. The other had been cyanosed on

effort since childhood, becoming deeply cyanosed with clubbing of the toes and fingers and marked polycythæmia in her fourth and fifth decades. She died at the age of 56 with extensive thrombosis and infarction in the pulmonary arterial tree. At autopsy a large patent ductus with great pulmonary arterial enlargement and great right ventricular hypertrophy was found in both patients. In the older patient gross calcification was present in the pulmonary artery, the ductus, and the aorta.

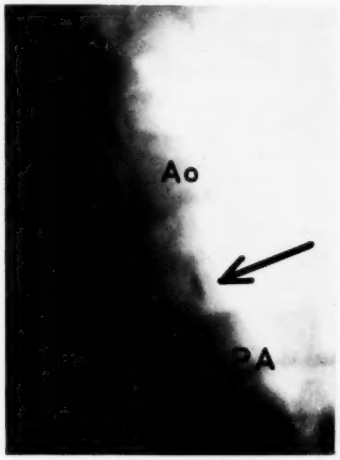


FIG. 1.—Portion of postero-anterior teleradiogram. Linear fleck of calcium (arrow) in the wall of a patent ductus in a patient with pulmonary hypertension. Ao=aorta. PA=pulmonary artery.

AUSCULTATION

In patent ductus two opposing streams crash head on within the pulmonary artery, one surging from the right ventricle upwards and backwards along its course, the other, a narrower powerful jet, projected by the high aortic pressure through the ductus into the pulmonary artery, where it meets the on-coming stream from the right ventricle. Since the pulmonary valve orifice is larger than that of the ductus and since a different course is taken by the two streams, the greater flow into the pulmonary artery in early systole is from the right ventricle. Later, as ventricular systole nears completion, the greater flow is from the ductus, and one may imagine turbulent eddies forming at this Watersmeet of the main pulmonary artery, until finally in diastole the flow is from the ductus alone. The typical murmur of patent ductus seems to mirror these events, for not only has it the continuous quality heard in murmurs due to arterio-venous shunts, but also, as it increases towards the end of systole and beginning of diastole, it is often punctuated by reverberations which vary from beat to beat as eddies swirl within the pulmonary artery.

A loud *continuous murmur* in the pulmonary area, in which there was no interruption between the systolic and diastolic components at the time of the second heart sound, was heard in all patients in the series with the exception of four with pulmonary hypertension. An accompanying thrill was felt in most patients. The phonocardiogram showed that the murmur varied in length and in about half the patients it was almost continuous throughout the cardiac cycle, while in the remaining half there was a gap of about one-tenth of a second between the first heart sound and the beginning of the murmur and a second gap of varying duration between the end of the murmur and the succeeding first heart sound. The murmur was shown to be loudest around and immediately before the second heart sound in 64 of the 69 patients (Fig. 2). Of the five patients who did not show this sign, one had pulmonary incompetence which persisted after ligation of the ductus and was thought to be due to a congenital abnormality of the pulmonary valve, one had aortic stenosis and incompetence, one was a child of eighteen months, while in the remaining two patients no cause for the different form of the murmur was apparent. The accentuation of the murmur around the second heart sound has been emphasized by many authors (Levine and Geremia, 1947; Evans, 1954; Haring *et al.*, 1954), since Gibson first described it in 1900.

In 34 patients with louder continuous murmurs, multiple clanging "*eddy sounds*", relatively localized to the pulmonary area, punctuated the systolic and diastolic portions of the continuous murmur (Fig. 3). The sounds varied from beat to beat, both in number and the exact place in the cardiac cycle, and in some beats they were altogether absent. In certain cycles as many as five such sounds were heard and it was difficult to recognize the true second heart sound amongst them without the aid of a phonocardiogram. These sounds were thought to be due to turbulent eddying currents set up in the main pulmonary artery and were most frequent in the second half of systole

and beginning of diastole, when the flow from the ductus becomes the dominant and later the sole source feeding the pulmonary artery. Eddy sounds were not thought to be related to the closure of the semilunar valves, since the sounds were often more than two in number, sometimes widely separated from the second heart sound, and because of their great intensity even in the absence of pulmonary hypertension. In addition, comparison of the pressure records obtained at catheterization and the phonocardiogram indicated that these eddy sounds sometimes preceded and sometimes

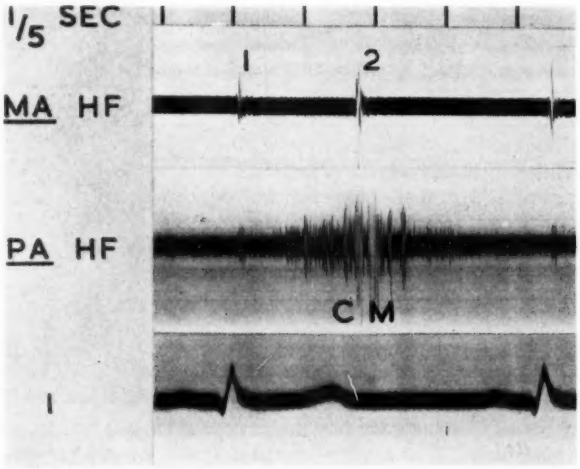


FIG. 2.—Phonocardiogram of the continuous murmur (CM) of patent ductus, loudest around the second heart sound (2). 1=first heart sound. MA and PA= mitral and pulmonary areas. HF=high frequency. 1=electrocardiographic lead 1.

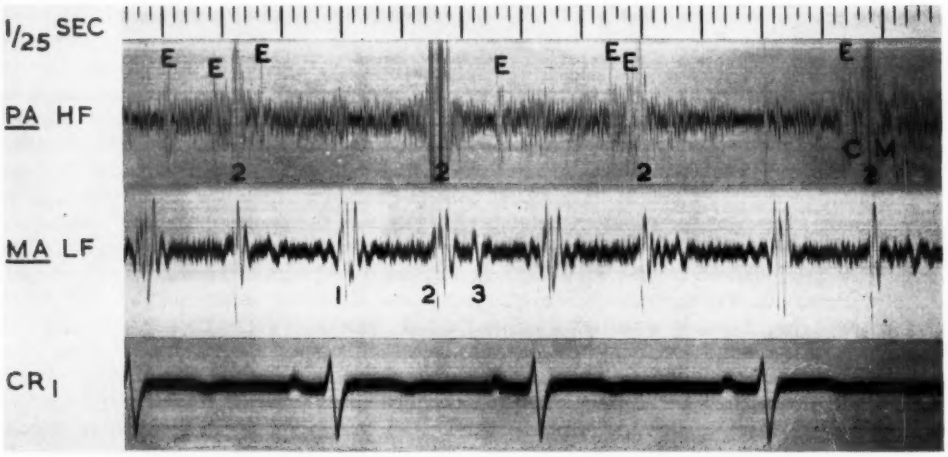


FIG. 3.—Eddy sounds (E), punctuating the continuous murmur (CM) of patent ductus in the pulmonary area. (PA). The timing and loudness of these sounds vary from beat to beat. 1, 2, and 3=first, second, and third heart sounds. MA=mitral area. HF and LF=high and low frequency. CR_1=electrocardiographic lead CR_1.

followed pulmonary and aortic valve closure, which could not, therefore, explain the sounds.

After ligation of the ductus the continuous murmur disappeared in all patients. It was often replaced by an insignificant and sometimes temporary systolic murmur in the pulmonary area, probably related to residual enlargement of the pulmonary artery.

The ductus is thought to have recanalized in the only two patients in whom the continuous murmur re-appeared after operation. In one of these the murmur returned within one month of operation, while in the other it was heard at the first attendance for review seven years later.

No *continuous murmur* was heard in the four patients with *severe pulmonary hypertension*. In the two patients with a reversed shunt, there was a soft early systolic murmur followed by an early diastolic murmur (Fig. 4A). In addition there was an atrial systolic murmur at the right sternal edge, probably due to a combination of right atrial hypertrophy and increased flow through the tricuspid valve due to the right-to-left shunt. Of the two patients in whom the pulmonary arterial pressure approached aortic pressure, one showed a soft early systolic murmur in the pulmonary area (Fig. 4B), while the second patient had a rough uneven systolic murmur followed by an early diastolic murmur (Fig. 4C). The early diastolic murmur was thought to be due to pulmonary regurgitation, resulting from dilatation of the pulmonary artery (Laubry, 1930). In the latter patient

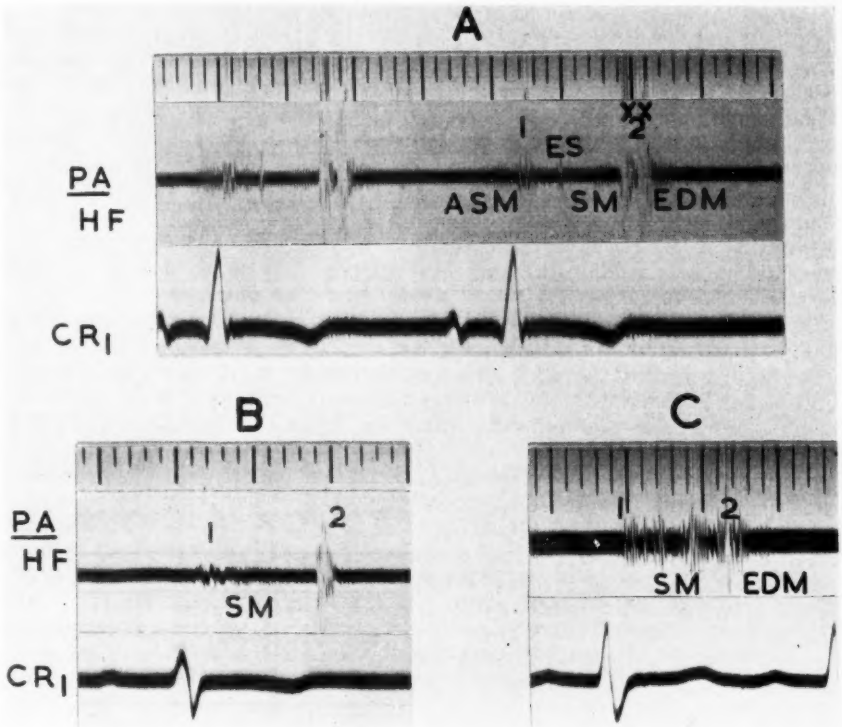


FIG. 4.—Absence of the continuous murmur in the pulmonary area (PA) in three patients (A, B, and C) with patent ductus complicated by pulmonary hypertension. Patient A had a reversed shunt. Patients B and C had balanced pressures. ASM=atrial systolic murmur. ES=ejection sound. SM=systolic murmur. EDM=early diastolic murmur. 1=first heart sound. 2xx=split second sound. HF=high frequency. CR_1=electrocardiographic lead CR_1.

it persisted for 48 hours after division of the ductus before disappearing permanently, this delay being presumably due to a gradual readjustment of pressures in the pulmonary circulation.

Mannheimer (1950) described four patients with proven patent ductus and pulmonary hypertension who had only a systolic murmur. Numerous reports have emphasized that there is no continuous murmur where pulmonary and aortic pressure levels approximate, either in adults with pulmonary hypertension (Wood, 1952; Hultgren *et al.*, 1953) or in infants with high pulmonary pressures and relatively low systemic pressures (Dammann and Sell, 1952; Ziegler, 1952; Bonham-Carter and Lovel, 1953). Although in an infant with a patent ductus a continuous murmur becomes more readily heard later, as the aortic pressure rises above that in the pulmonary artery (Gilchrist, 1945), the converse, namely the disappearance of a continuous murmur with increasing pulmonary hypertension, is rare (Campbell and Hudson, 1952).

The *second heart sound*, which is enveloped in the continuous murmur, was often difficult to analyse in detail. In 11 patients the phonocardiogram showed that the sound was clearly split, an interval of 0·03 to 0·04 sec. separating the two components, while in six patients it was clearly single. None of these patients had significant pulmonary hypertension and hence the pulmonary component of the second heart sound was not accentuated. Of the two patients with *a reversed shunt*, in one the second heart sound was widely split, the second or pulmonary component being very loud (Fig. 4A), while in the other the second sound was loud and single. Of the two patients with a "*balanced ductus*", in whom the pulmonary arterial pressure approached that in the aorta, in one the second sound was very loud and single (Fig. 4B), while reversed splitting of the second sound was thought to be present in the other patient, pulmonary valve closure preceding aortic valve closure in the phonocardiogram, as described by Gray (1956). In the latter patient we believe delayed aortic valve closure to have resulted from a conduction delay in the left ventricle, the electrocardiogram showing great left ventricular preponderance with broadening and notching of the QRS complex, which was 0·1 sec. wide. It is unlikely to have been directly related to increased left ventricular stroke output resulting from the large left-to-right shunt, since reversed splitting of the second sound persisted after ligation of the ductus.

In 34 patients eddy sounds made it impossible to recognize with certainty splitting of the second heart sound and in a further 18 patients the second sound could not be analysed in detail, since it was obscured by the murmur.

An *ejection sound* over the base of the heart, as described by Leatham and Vogelpoel (1954), was heard in three patients, of whom two (Fig. 4A) had aneurysmal dilatation of the pulmonary artery with pulmonary hypertension and the third enlargement of the ascending aorta due to coarctation. An ejection sound in patent ductus with a large pulmonary artery may be more frequent than we have found it, but its recognition in our patients was rendered difficult by the beginning of the continuous murmur.

A *third heart sound* was present in 33 of the 52 patients in whom a low-frequency phonocardiogram was recorded in the mitral area, but it was sometimes difficult to detect clinically owing to the intensity of the continuous murmur. The high incidence of a third heart sound in this series was expected, since 40 of the 52 patients were below the age of 25 and Evans (1943) showed a third heart sound to be a relatively common finding in healthy subjects in this age group. None of the patients over the age of 40 had a third heart sound.

An *apical mid-diastolic murmur* was present in 8 of the 22 patients with a large left-to-right shunt through the ductus (Fig. 5). The mid-diastolic murmur was usually soft and never of more than moderate intensity, and resembled in character a soft rumbling murmur of mitral stenosis. It was never accompanied by a thrill. It varied in length, averaging about 0·15 sec., although in one patient it was only 0·08 sec. long. The timing of the murmur was in mid-diastole, although in one patient this coincided with atrial systole, due to tachycardia. All the patients with a mid-diastolic murmur also had an apical systolic murmur.

A distant *snap-like* sound preceded the mid-diastolic murmur in five of these eight patients (Fig. 5). It resembled, both in character and in its place in the cardiac cycle, a distant opening snap

of mitral stenosis, although it was usually best heard a little further out towards the apex. The interval between the beginning of the second heart sound and the snap lay between 0·06 and 0·1 sec., which is within the range (0·03 to 0·14 sec.) found in mitral stenosis (Mounsey, 1953). The mid-diastolic murmur immediately followed the snap in three patients, and after an interval of 0·05 sec. in the remaining two. In addition to the snap a third heart sound was seen in the low-frequency phonocardiogram in all eight patients and in two of them it was abnormally large.

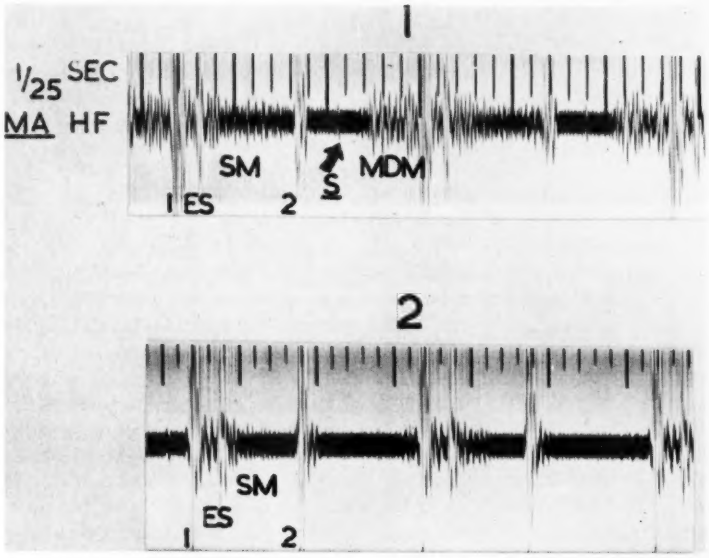


FIG. 5.—Phonocardiograms of the same patient (1) before and (2) after ligation of a patent ductus with a large left-to-right shunt. The snap (S) and mid-diastolic murmur (MDM) in the mitral area (MA) have disappeared after operation. 1 and 2=first and second heart sounds. ES=ejection sound. SM=systolic murmur. HF=high frequency.

After ligation of the ductus the mid-diastolic murmur and snap disappeared in seven of the eight patients (Fig. 5). The apical systolic murmur became softer, but it was never abolished completely. The abnormally large third heart sound in two patients disappeared.

The disappearance of the mid-diastolic murmur and snap in seven of the eight patients after operation indicated that these signs were not due to mitral stenosis, but resulted from increased flow through the mitral valve. Further support is lent to this theory by the presence of a large third heart sound in two of the patients, which is never found in tight mitral stenosis. Turbulent flow murmurs are well recognized (Nadas and Alimurung, 1952) and have been described in ventricular defect and patent ductus (Ravin and Darley, 1950). The origin of the snap is less clear. Whether it is produced at the mitral valve, and, if so, whether a healthy mitral valve can give rise to a snap in the presence of increased blood flow or whether some abnormality or scarring of the valve is necessary in addition is open to speculation. Leatham and Gray (1956) suggested that a similar snap sound and diastolic murmur may be produced at the tricuspid valve under conditions of increased blood flow in atrial septal defect.

The *simulation of mitral stenosis* in patent ductus with a large shunt has been referred to by Vernant *et al.* (1955) as the *syndrome pseudo-mitrale*. They found a mid-diastolic murmur, a rather abrupt first sound, fullness of the left atrium, bifid P waves, and a raised pulmonary capillary

pressure in some of their patients with a large shunt. They did not, however, comment on a snap sound. The mid-diastolic murmur disappeared after operation in all their patients, and the pulmonary capillary pressure returned to normal in those who were examined by cardiac catheterization after operation. Their conclusion was that increased blood flow through the mitral valve in patent ductus may give rise to relative mitral stenosis. In our series one patient with a snap and mid-diastolic murmur was found to have a raised pulmonary capillary pressure (15/12 mm. Hg) and both snap and murmur disappeared after operation. A mid-diastolic murmur was associated with fullness of the left atrium in two of our patients with a large shunt, and five had bifid P waves. The association of a snap sound with a mid-diastolic murmur in five of our patients further emphasizes the close similarity between the clinical signs of a large shunt in patent ductus and those of mitral stenosis.

Associated Heart Disease

Aortic valve disease, coarctation of the aorta, ventricular septal defect, and pulmonary stenosis are the conditions most frequently met in association with patent ductus and examples of each were seen in our series of patients. Of the nine patients with associated heart lesions, two had coarctation of the aorta (one with a large aneurysm distal to it), one ventricular defect, one aortic stenosis, three aortic stenosis and incompetence, one simple pulmonary stenosis, and one pulmonary incompetence. An additional murmur, or the absence of the femoral pulse, made it possible in most patients to recognize the associated lesion and we were thus able to warn the patients before operation that surgery would not effect a complete cure. Where the continuous murmur was loud, it was not always easy to recognize the additional lesion. Thus, in the three patients with aortic stenosis and incompetence, the soft early diastolic murmur was only recognized before operation in one. The characteristic loud systolic murmur of aortic stenosis, with a gap before the second heart sound on the other hand (Alzamora-Castro *et al.*, 1948; Levine, 1949; Leatham, 1951), could be clearly made out in the aortic area both in these three patients and in the patient with lone aortic stenosis. In another patient mild pulmonary stenosis was only diagnosed after operation. In the patient with a ventricular septal defect and patent ductus the clinical signs suggested the double diagnosis, which was later confirmed by cardiac catheterization and by the persistence of the pansystolic murmur and thrill following ligation of the ductus.

Differential Diagnosis of the Continuous Murmur

Since the continuous murmur holds pride of place in the diagnosis of patent ductus, there is need to compare its timing and quality with continuous murmurs due to other causes. The continuous murmur arising from bronchial arteries in pulmonary atresia, systemic and pulmonary arterio-venous aneurysms, and collateral arteries in coarctation were examined. All of these resembled patent ductus in that the murmur was loudest around the second heart sound, but its time of onset differed (Fig. 6) and it appeared to be related to the site in the circulation where the murmur was produced. Thus in pattern and timing the murmur of patent ductus and that arising from bronchial arteries in pulmonary atresia were similar: in systemic and pulmonary arterio-venous fistula and collateral arteries in coarctation, on the other hand, the crescendo to the murmur started later, the delay being probably due to the increased time taken by the pulse wave to reach the affected vessel. The murmur of venous hum differed from other continuous murmurs in that it was not loudest around the second heart sound, there being a crescendo in mid-diastole when rapid venous filling of the heart was taking place (Fig. 7). These lesions, however, seldom present a diagnostic problem, since the site where the murmur is best heard and the general clinical picture usually exclude patent ductus. Defects of the aortic and bulbar septa and abnormal coronary vessels, on the other hand, may sometimes be very difficult to distinguish clinically from patent ductus, and a description of three such patients is given below.

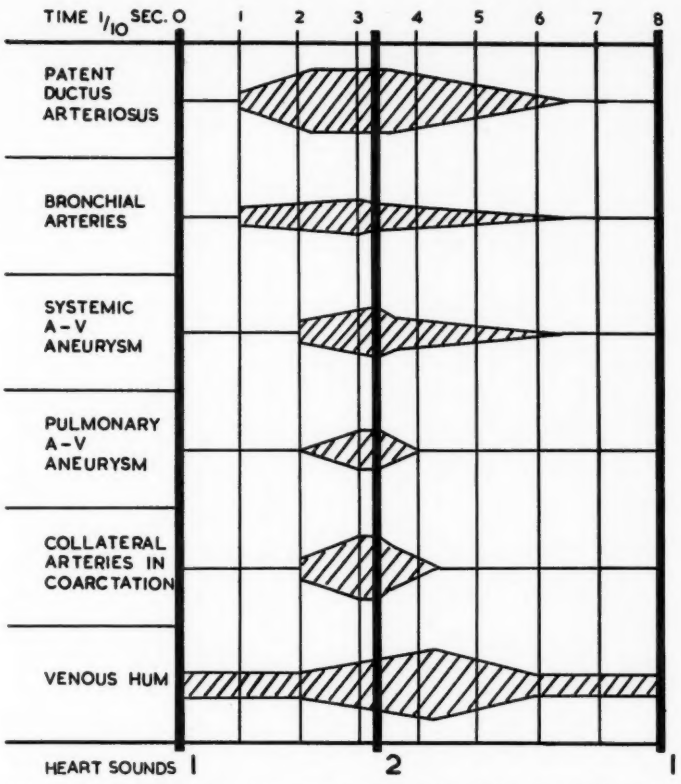


FIG. 6.—Diagram of phonocardiograms illustrating the relative place in the cardiac cycle of continuous murmurs due to different causes. The timing of a venous hum is also shown. The heavy vertical lines indicate the first and second heart sounds.

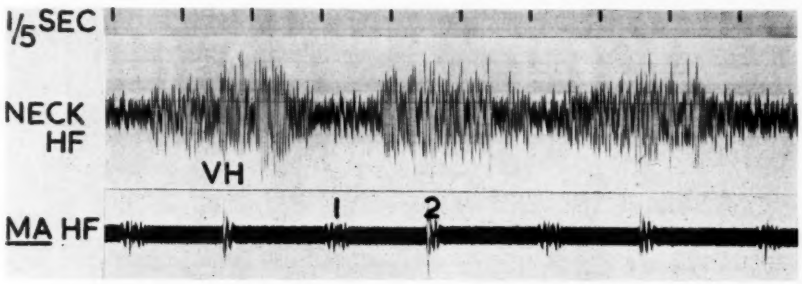


FIG. 7.—Venous hum (VH) recorded in the neck. 1 and 2=first and second heart sounds. MA=mitral area. HF=high frequency.

Six Patients in whom No Patent Ductus was Found

There were six patients in this series in whom thoracotomy was undertaken and no patent ductus found, but in only two of these was the continuous murmur completely typical of patent ductus. Three of the patients have not been further investigated since they have few symptoms. Their operations were performed between six and nine years ago and in view of their unusual murmurs a ductus would probably now have been excluded by cardiac catheterization rather than by an exploratory thoracotomy. Of the remaining three patients, a diagnosis of aorto-pulmonary septal defect was made at thoracotomy in one, while two have since been further investigated.

The patient believed to have an *aorto-pulmonary septal defect* is of special interest due to the progressive change in cardiac murmurs. She had at the age of four a continuous murmur, best heard in the pulmonary area and loudest around the second heart sound, typical in all respects of a patent ductus (Fig. 8). At thoracotomy no patent ductus was found, but there was a thrill low

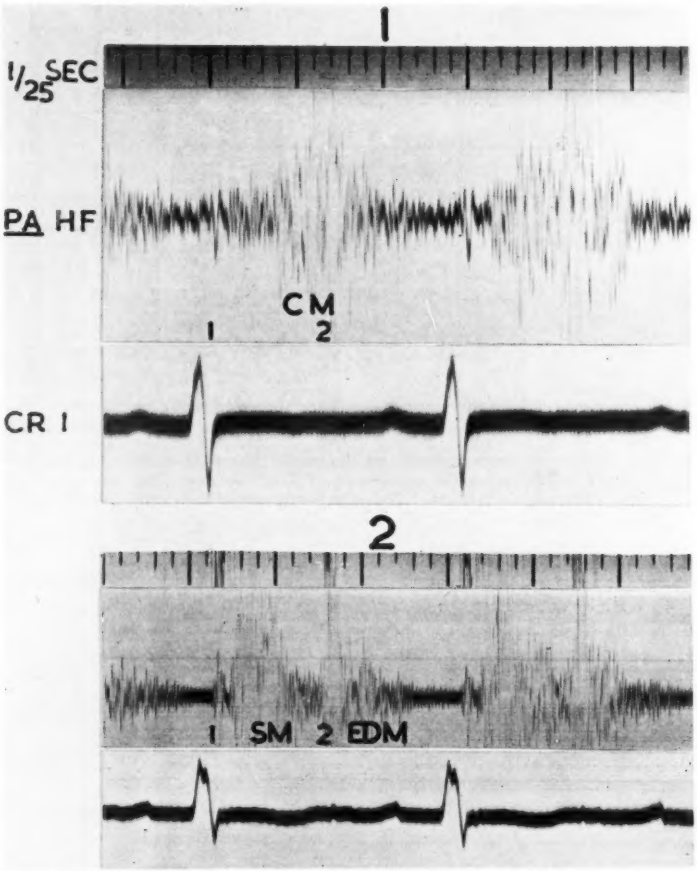


Fig. 8.—Phonocardiograms of the same patient, (1) aged four years and (2) aged eight, who is believed to have an aorto-pulmonary septal defect. Replacement of a continuous murmur (CM) in the pulmonary area (PA) by a systolic murmur (SM) and an early diastolic murmur (EDM). 1 and 2=first and second heart sounds. HF=high frequency. CR_1=electrocardiographic lead CR_1.

down near the base of the aorta and pulmonary artery, which was greatly enlarged. A diagnosis of aorto-pulmonary septal defect was made and it was decided not to attempt closure of the defect at that time. She has now been followed for four years since thoracotomy and the continuous murmur has been replaced by a systolic and early diastolic murmur (Fig. 8). Progressive electrocardiographic and radiological changes suggest that the alteration in the murmur is due to increasing pulmonary hypertension. Permission for cardiac catheterization has so far been refused.

An *aorto-right-ventricular fistula* was the cause of the continuous murmur in a man, aged 58 years. A cardiac murmur was first heard at the age of 11, and a continuous murmur had been known to be present since the age of 28 years. He had an obvious Corrigan pulse with vigorous pulsation of both aorta and pulmonary artery on screening and some left ventricular enlargement. There was a prominent thrill localized at the fourth space between the sternum and the apex beat. The murmur, which was superficial, very loud, and continuous, was greatest in mid-systole, waned around the second heart sound, and waxed again in mid-diastole (Fig. 9). It thus differed in site

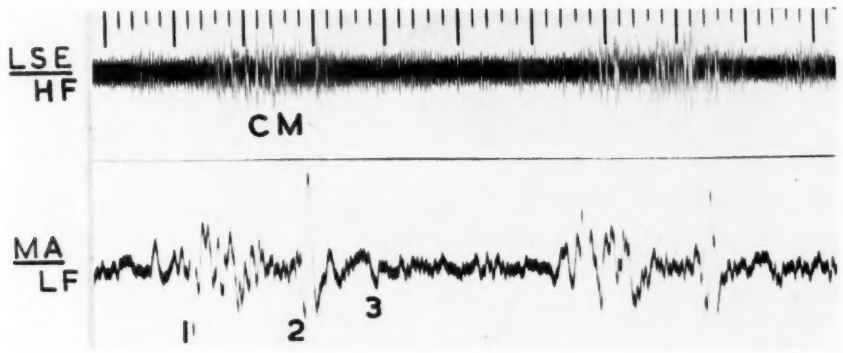


FIG. 9.—Continuous murmur (CM) in the fourth intercostal space at the left sternal edge (LSE) in a patient with an aorto-right-ventricular fistula. The murmur is not clearly loudest around the second heart sound (2). 1 and 3=first and third heart sounds. MA=mitral area. HF and LF=high and low frequency.

and timing from the characteristic murmur of patent ductus. At the first thoracotomy in 1945 no patent ductus was found, but following this, the patient complained of considerable anterior chest pain, which he stated was continuous and prevented him from working. In 1955, in view of the persistence of pain and continued evidence of intra-cardiac shunt, it was decided to investigate him further. Angiocardiography showed an anomalous channel arising anteriorly from the aorta and refilling of the pulmonary artery, simultaneously with aortic filling. Cardiac catheterization indicated a small left-to-right shunt in the upper part of the right ventricle. At the second thoracotomy, the abnormal channel was found to be within the right ventricular wall and appeared to be fed from an aneurysm of the sinus of Valsalva. The thrill diminished following insertion of five deep ligatures into the right ventricular muscle, but the channel could not be completely occluded. Its nature remains uncertain, but it is probably a congenital cardio-aortic fistula associated with an aneurysm of the sinus of Valsalva. The patient declares that his chest pain has been removed by the second operation, but the physical signs in the heart are unchanged. Jones and Langley (1949) in a review of the reported cases of cardio-aortic fistula noted that, where the fistula appeared from the history to be congenital, the condition was sometimes compatible with quite a long span of life, one patient dying at the age of 51 years from intercurrent disease. More recently Brown *et al.* (1955) reported a case of cardio-aortic fistula, which was closed by open heart surgery, after which the patient unfortunately died.

A *coronary-right-ventricular fistula* was the cause of the continuous murmur in a woman, aged 56, who presented with recent congestive failure after a very active life. A cardiac murmur was first heard at the age of 18, but there is no record of its nature at that time. The continuous murmur did not show definite accentuation around the second heart sound, but it was otherwise typical of patent ductus in site and quality (Fig. 10). There was left ventricular enlargement on screening

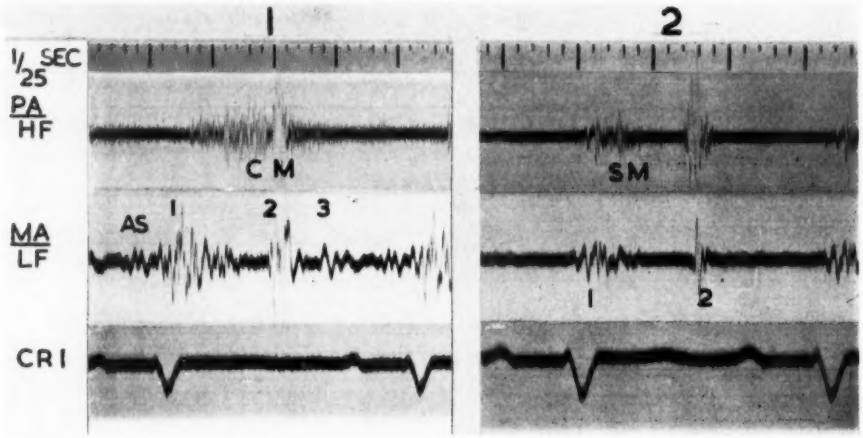


FIG. 10.—Phonocardiograms of the same patient, (1) before and (2) after ligation of a coronary-right-ventricular fistula. The continuous murmur (CM) in the pulmonary area (PA) has disappeared after operation and only a small murmur (SM) remains. AS=atrial sound. 1, 2, and 3=first, second, and third heart sounds. MA=mitral area. HF and LF=high and low frequency. CR_1=electrocardiographic lead CR_1.

and the main pulmonary arteries were enlarged and vigorously pulsating. The electrocardiogram showed considerable left ventricular preponderance. The pulse was full and the blood pressure 180/100 mm. Hg. A moderate increase in pulmonary arterial pressure was found at cardiac catheterization (70/25 mm. Hg) and there was evidence of a small left-to-right shunt in the pulmonary artery, but no shunt was demonstrated in the right ventricle. No patent ductus was found at thoracotomy, but large tortuous coronary arteries were seen and it was thought that the lesion might be a coronary anomaly similar to that described by Baylis and Campbell (1952) and by Davis *et al.* (1956), in which a branch of the left coronary artery entered the right ventricle. A subsequent angiocardiogram showed refilling of the pulmonary artery and in the lateral view an abnormal dilated tortuous coronary artery filling from the aorta (Fig. 11). At a second thoracotomy a dilated branch of the left coronary artery entering the conus of the right ventricle was ligated and the continuous murmur immediately disappeared (Fig. 10). It was noted, however, at both operations, that the whole coronary arterial tree appeared to be dilated and tortuous so that the shunt between the left coronary artery and the right ventricle may not have been the sole coronary anomaly. The initial improvement following operation has not been maintained, in spite of the permanent disappearance of the continuous murmur, and the patient remains in chronic congestive failure.

The simulation of the continuous murmur and general clinical picture of patent ductus by a high ventricular septal defect with aortic incompetence, due to a sagging aortic valve cusp, has been discussed by Gross and Longino (1951), Wood *et al.* (1954), and Bonham-Carter and Walker (1955), but no example of this condition has been proven among our patients.

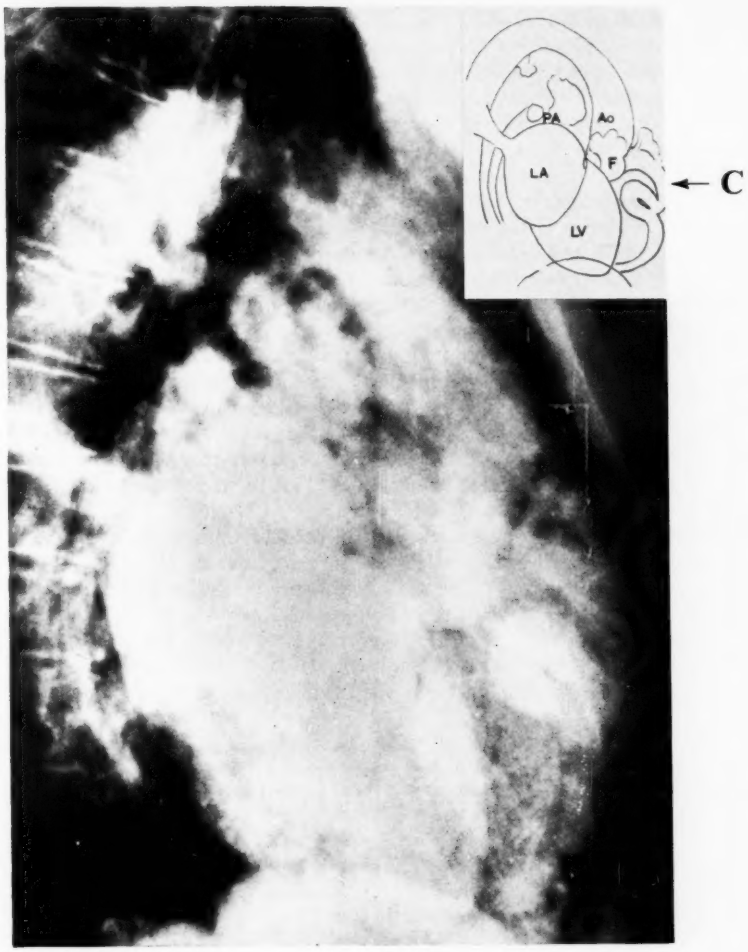


FIG. 11.—Angiocardiogram of patient with a coronary-right-ventricular fistula. A dilated, tortuous coronary artery (C) is seen anteriorly, while posterior to it is another coronary branch (F), which is probably the fistula entering the right ventricle, through which refilling of the pulmonary artery (PA) is taking place. LV=left ventricle. LA=left atrium. Ao=aorta. Angiocardiogram in left lateral position.

SUMMARY AND CONCLUSIONS

The auscultatory signs have been examined clinically and in the phonocardiogram in 73 patients with patent ductus arteriosus. The diagnosis was confirmed at operation in 71 patients and at autopsy in the remaining two.

In the absence of significant pulmonary hypertension a continuous murmur was always present. It was best heard in the pulmonary area and in 64 of the 69 patients it was loudest around the second heart sound.

Multiple eddy sounds were a feature of the murmur and were sometimes difficult to differentiate from the second heart sound.

In the four patients in whom the pulmonary artery pressure equalled or exceeded that in the aorta the continuous murmur was curtailed to a relatively soft systolic murmur; in three there was an early diastolic murmur from added pulmonary regurgitation.

A large left-to-right shunt through the ductus was judged to be present in 22 of the patients and in 8 of these there was an apical mid-diastolic murmur. In addition a distant snap sound preceded the mid-diastolic murmur in five of these eight patients. After ligation of the ductus, the mid-diastolic murmur and snap disappeared in all but one. Where the murmur and snap disappeared after abolition of the shunt, these signs were thought to arise from an increased flow through the mitral valve and did not indicate mitral stenosis.

In the two patients with a reversed shunt through the ductus due to pulmonary hypertension, an atrial systolic murmur was heard at the right sternal edge.

Aortic valve disease, coarctation of the aorta, ventricular septal defect, and pulmonary stenosis were the conditions met in association with patent ductus. An additional murmur, or the absence of the femoral pulse, made it possible, in most patients, to recognize the associated lesion before ligation of the ductus.

Continuous murmurs due to systemic and pulmonary arterio-venous aneurysm and to bronchial arteries in pulmonary atresia were found to show the same accentuation around the second heart sound as the characteristic murmur of patent ductus, but the crescendo to the murmur started later in arterio-venous aneurysm.

In the period during which these patients with patent ductus were seen six other patients were submitted to thoracotomy, without a patent ductus being found. The continuous murmur differed from the characteristic murmur of patent ductus in site or timing in four of the six patients, including one with an aorto-right-ventricular fistula, the diagnosis in the other three remaining uncertain. In the remaining two patients, however, one of whom had a coronary-right-ventricular fistula and the other a suspected aorto-pulmonary septal defect, neither the site, character, or timing of the continuous murmur distinguished the condition from patent ductus arteriosus.

We wish to express our sincere thanks to Dr. William Evans and Dr. Wallace Brigden for their help and criticism in the preparation of this paper and to Mr. Vernon Thompson and Mr. Geoffrey Flavell, who performed the operations, for their advice and encouragement. We also wish to thank Dr. L. J. Rae and the staff of the radiodiagnostic department for their help with the angiocardiogram. Thanks are also due to Mr. William Dicks for technical help.

REFERENCES

Alzamora-Castro, V., Rubio W., C., and Battilana D., G. (1948). *Rev. argent. Cardiol.*, **15**, 25.
Baylis, J. H., and Campbell, M. (1952). *Guy's Hosp. Rep.*, **101**, 174.
Bonham-Carter, R. E., and Lovel, K. W. (1953). *Great Ormond St. J.*, **6**, 93.
—— and Walker, C. H. M. (1955). *Lancet*, **268**, 272.
Brown, J. W., Heath, D., and Whitaker, W. (1955). *Circulation*, **12**, 819.
Campbell, M., and Hudson, R. (1952). *Guy's Hosp. Rep.*, **101**, 32.
Cosh, J. A. (1953). *Brit. Heart J.*, **15**, 423.
Dammann, J. F., and Sell, C. G. R. (1952). *Circulation*, **6**, 110.
——, Berthrong, M., and Bing, R. J. (1953). *Johns Hopk. Hosp. Bull.*, **92**, 128.
Davis, C., Fell, E. H., Gasul, B. M., and Dillon, R. (1956). *Arch. Surg., Chicago*, **72**, 838.
Evans, W. (1943). *Brit. Heart J.*, **5**, 205.
—— (1954). *Cardiography*. Butterworth, London.
Gibson, G. A. (1900). *Edinb. med. J.*, **8**, 1.
Gilchrist, A. R. (1945). *Brit. Heart. J.*, **7**, 1.
Gray, I. (1956). *Brit. Heart J.*, **18**, 21.
Gross, R. E., and Longino, L. A. (1951). *Circulation*, **3**, 125.
Haring, O. M., Luisada, A. A., and Gasul, B. M. (1954). *Circulation*, **10**, 501.
Hultgren, H., Selzer, A., Purdy, A., Holman, E., and Gerbode, F. (1953). *Circulation*, **8**, 15.
Johnson, R. E., Wermer, P., Kuschner, M., and Cournand, A. (1950). *Circulation*, **1**, 1293.
Jones, A. M., and Langley, F. A. (1949). *Brit. Heart J.*, **11**, 325.
Laubry, C. (1930). *Nouveau Traité de Pathologie interne*. 111. Doin, Paris.

Leatham, A. (1951). *Brit. Heart. J.*, **13**, 153.
—— and Gray, L. (1956). *Brit. Heart J.*, **18**, 193.
—— and Vogelpoel, L. (1954). *Brit. Heart J.*, **16**, 21.
Levine, S. A., and Geremia, A. E. (1947). *Amer. J. med. Sci.*, **213**, 385.
—— (1949). *Clinical Auscultation of the Heart.* Saunders, Philadelphia and London.
Mannheimer, E. (1950). *Arch. Mal. Cœur.*, **43**, 324.
Mounsey, J. P. D. (1953). *Brit. Heart J.*, **15**, 135.
Nadas, A. S., and Alimurung, M. M. (1952). *Amer. Heart J.*, **43**, 691.
Ravin, A., and Darley, W. (1950). *Ann. intern. Med.*, **33**, 903.
Vernant, P., Nouaille, J., Schweisguth, O., Labesse, J., Bouchard, F., Mathey, J., Binet, J. P., and Oustrières, G. O. (1955). *Arch. Mal. Cœur*, **48**, 277.
Wood, P. (1952). *Brit. med. Bull.*, **8**, 348.
——, Magidson, O., and Wilson, P. A. O. (1954). *Brit. Heart J.*, **16**, 387.
Ziegler, R. F. (1952). *Amer. Heart J.*, **43**, 553.

RESTENOSIS OF THE MITRAL VALVE

BY

J. R. BELCHER

From the London Chest and Middlesex Hospitals

Received May 20, 1957

Does restenosis of the mitral valve occur? Glover (1955) says categorically that it does not. A critical survey of published cases suggests that if restenosis is defined as refusion of the commissures after their complete separation, then it is rare. Generally the original operation was inadequate, and in fact there is no case recorded in which restenosis occurred after complete division of the commissures. On the other hand, if the definition of restenosis is extended to include all cases in which the valve orifice has become smaller after dilatation or partial division, then the entity is not uncommon.

When valvotomy has been inadequate, that is where the separation of the commissures has not been carried beyond the critical area of tendon insertion (Brock, 1952), temporary and often considerable improvement in the patient's symptoms has been achieved. Even a small increase in the size of the mitral orifice may lead to a disproportionately large increase in the exercise tolerance. This amelioration has often been short-lived, because the raw edges of the cusps remain close to each other in all phases of the cardiac cycle and are hence liable to become readherent.

The refusion of completely opened commissures is a different problem. As the cusp edges can become widely separated during ventricular filling, particularly if the chordæ tendineæ are not matted together (Cooley, 1951), there may be a long interval before the restenosis develops. Possibly the only cause of readherence is a recrudescence of the rheumatic process: this suggestion is supported by the fact that in the few cases of this type reported, a history of reactivation has been given in five (McKusick, 1955; Glenn, 1956; Donzelot *et al.*, 1953; Dussailant, 1954; and Morino, 1955). In the four cases in this series there was a history of sub-acute bacterial endocarditis in one.

As the pathology of the two varieties of recurrence of mitral stenosis is different, confusion may be avoided if they are called " true " and " false " restenosis. True restenosis will be used to refer to that which occurs after one or both commissures have been completely opened; and false restenosis, to that which occurs where neither commissure has been divided beyond the area of insertion of the papillary muscles.

Incidence

At the Henry Ford symposium (Lam, 1955) the problem of restenosis was discussed, but despite the large experience of the speakers few cases were described. Brock reported four cases in a series of 350, Keyes had one in 180, and Harken said he had had 10 in 800 patients. Few details were given, but Harken said that 9 of his 10 patients had had inadequate division of the commissures originally.

Baker *et al.* (1955) in an analysis of 45 patients who had been followed for more than three years, found that 15 per cent deteriorated after an initial improvement, but did not refer specifically to restenosis. Glover (1955) found no evidence of restenosis in 41 of 50 patients living five years after operation. Sellors *et al.* (1953) did not mention the condition in their analysis of 111 cases, nor did Goodwin *et al.* (1955), although they did describe a patient who died 15 months after operation and who was found to have a tightly stenosed and calcified valve. Turner and Fraser

(1956) refer to four cases of restenosis in a series of 250, but in each of these the original valvotomy was inadequate. Wood (1956) has said that true restenosis occurs in 2 per cent per year of patients subjected to valvotomy, but he makes the point that as the natural history of mitral valve disease spreads over a period of fifteen years, the true incidence of restenosis will not be known for some years to come Wood (1954).

The evidence for restenosis in the reported cases has been based either on post-mortem findings or on examination of the valve at a second operation (Table I). Some authors in searching for evidence of restenosis have found none (Glover, 1955, and Muller, 1952). Yet others have described cases where the evidence was based on reappearance of the diastolic murmur (Canigia, 1955) or where the stenosis was found to be at the level of the chordæ tendineæ (Jordan, and Hellems, 1952). These have not been included in the table as the evidence was not thought to be strong enough to call them examples of restenosis. It will be seen that few cases of true restenosis have been described: there is no case in which both commissures were fully split.

TABLE I

SUMMARY OF THE REPORTED CASES OF RESTENOSIS

Author	Age	Sex	Reoperation or necropsy	Type	Comment
McKusick	37	M	Necropsy	True	Rheumatic
Glenn and Dineen ..	39	M	Re-operation	True	Rheumatic
Morino	28	M	,,	True	Rheumatic
Keyes and Lam ..	29	M	,,	True	No history of R.F.
Donezolot *et al.* ..	29	M	Necropsy	True	Rheumatic
Dussailant	?	?	,,	True	Rheumatic
Santy *et al.*	26	F	Re-operation	True	? cause
Bailey	41	F	,,	False	Calcified valve
Baden and Therkelsen	41	M	,,	False	Elastic valve
Baronofsky *et al.* ..	43	F	,,	False	
,, ,, ,, ..	43	F	,,	?	No details

CASE REPORTS

Case 1. E. S., a woman, aged 40, had severe disability, and a history of paroxysmal nocturnal dyspnœa. At operation she was found to have a moderately mobile valve; the circumference of the orifice was 4 cm.; there was no calcification, but only a poor split was achieved. The final orifice had a circumference of 6 cm. and there was no mitral regurgitation.

After the operation a fair result was recorded. She had one episode of congestive cardiac failure during the next 8 months, but her improvement was maintained. After this her condition deteriorated and she was readmitted two years after the original operation with as severe disability as she had had originally. At operation the valve was approached via the atrial wall as the appendage had been amputated at the first operation. Little restenosis had occurred, but slight incompetence was present. On this occasion the lateral commissure was completely split without an increase in the regurgitation.

When she was seen six months after her second operation, she was better than she had ever been, and was classed as a good result.

Case 2. T. T., a woman, aged 42, had some years previously had a thyroidectomy for mitral stenosis; despite this she had severe disability and a history of recent congestive cardiac failure. At operation she was found to have a heavily calcified valve with a 4-cm. orifice. A minor degree of dilatation only was achieved.

For six months after this she enjoyed a slightly increased exercise tolerance, but then she returned to her original state and had repeated attacks of cardiac failure. She was readmitted four years after her operation for a second valvotomy. At operation the trans-atrial approach had to be used. The valve orifice was found to be 4·5 cm. in circumference, this being a little less than at the end of the first operation. Efforts to increase the orifice by the usual methods failed. The method of trans-ventricular dilatation described by Logan (1955) was therefore used. By this means it was possible to rupture the calcified commissures, and the final circumference of the orifice was at least 8 cm.

Immediately after the operation the signs of mitral stenosis had almost disappeared, and six months later her exercise tolerance was greatly improved, all signs of cardiac failure had gone, and she was classed as a good result.

Case 3. F. M., a man, aged 40, had a three-year history of increasing dyspnœa, and now had moderate disability. At operation heavy calcification was found along the lateral commissure, but the remainder of the valve was mobile. The orifice was 4 cm. in circumference. The medial commissure was partially split leaving a poor opening. No impression could be made on the lateral commissure at this time.

He was somewhat better after his operation, but this improvement only lasted for six months. Thereafter he reverted to his pre-operative state, and later deteriorated still further. He was readmitted three years after the first operation. His disability was now severe, and he had functional tricuspid incompetence. At operation, the valve was approached via the atrial wall. He was found to have slight mitral incompetence, but otherwise the condition of the valve seemed identical with that described at the end of the first operation. On this occasion a full split of both commissures was achieved by the use of the dilator inserted through the ventricle; the blades were opened until they were 5 cm. apart.

There was an immediate change in his physical signs and all those of mitral stenosis disappeared. When last seen his exercise tolerance was greatly improved and a good result was recorded.

Case 4. E. W., a woman, aged 39, had a two-year history of increasing dyspnœa, of repeated attacks of angina pectoris, and of paroxysmal nocturnal dyspnœa. Her disability was severe. At operation she was found to have a mobile valve with an orifice 3·5 cm. in circumference. There was slight mitral regurgitation. The commissures were both heavily calcified and only a poor split was achieved, the final orifice being 5 cm. in circumference.

There was some improvement in her exercise tolerance for four months, but after this she deteriorated gradually and on readmission 18 months after the first operation she was worse than she had ever been.

At operation the valve was approached through the atrial wall, the orifice was found to be 5 cm. in circumference, and the regurgitation persisted unaltered. On this occasion the valve was successfully split using the transventricular route; the final circumference of the orifice was 8 cm.

Four months later, she had improved considerably more than before; the diastolic murmur was short and quiet, and she was classed as a good result.

Case 5. R. R., a woman, aged 40, had had bronchitis and increasing dyspnœa for the last six years. On admission her disability was severe. At operation the appendage was found to be shrivelled up and the approach had therefore to be made via the atrial wall. The valve was mobile and elastic, there was no calcification, and the orifice had a circumference of 3 cm. A poor split only was achieved.

For a month after her operation there was slight improvement of her exercise tolerance, but then she deteriorated to her condition before operation.

She was readmitted two years after her first operation and a second attempt was made via the atrial wall. Again she was found to have a tight stenosis with a valve orifice of 3·5 cm. circumference. An attempt was made to split the commissures by the transventricular route, but despite wide opening of the dilator, the elastic property of the valve prevented a proper split: the final orifice was estimated as only 6 cm. Very little improvement followed this operation and she now has severe cardiac failure again. She died from a cerebal embolas three months after a third operation.

Case 6. P. B., a woman, aged 36, had a moderate disability (Grade 2) and she was orthopnœic. At operation the valve was found to be mobile, a moderate degree of incompetence was present, and the stenosis was by no means tight (5 cm. circumference). Both defects were thought to be contributing to her disability. A partial split of the anterolateral commissure was done and the final orifice had a circumference of 6·5 cm.

Her convalescence was prolonged and very little improvement was achieved by the operation. After one year she was as bad as ever. She was readmitted six months later with signs of considerable mitral stenosis, but of little incompetence. At operation the valve was approached via the atrial wall. The orifice had decreased little (circumference 5·5 cm.) and as finger fracture was found to be impossible, a transventricular valvotomy was done. Both commissures were thus fully opened, but the dilator became caught in the chordæ and the incompetence was increased. Despite this the patient made a good recovery and when last seen her exercise tolerance was improved.

Case 7. I. B., a woman, aged 26, gave a history of increasing dyspnœa and was severely disabled (Grade 3). There was functional tricuspid incompetence. At operation the valve was approached via the atrial wall as the appendage had no lumen. Extensive loose clot was encountered in the atrial cavity. There was tight stenosis of the valve and it was heavily calcified. Little increase in the orifice was achieved on this occasion (final circumference 4 cm. instead of 3 cm.). After operation she had a cerebral embolus, from which she made a slow but almost complete recovery.

A surprising amount of improvement in the exercise tolerance was achieved by this inadequate operation, and she was classed as a good result for 18 months. After that she deteriorated and was readmitted one year later. By then her disability was as bad as ever and she had congestive cardiac failure. She had signs of tight mitral stenosis and of tricuspid incompetence.

At operation the valve was again approached via the atrial wall. The orifice was again found to be 3 cm. in circumference but there was no incompetence. No impression could be made on the stenosed valve with a finger, but an almost complete split of both commissures was achieved via the ventricle (9 cm. circumference). Her exercise tolerance was improved.

Case 8. M. E., a woman, aged 37, had severe disability (Grade 3) and she was orthopnœic. At operation she was found to have moderate stenosis, the valve being mobile and not calcified. Only a poor split was made, the postero-medial commissure being almost completely opened. The other commissure could not be split.

A fair degree of improvement only was achieved and this was maintained for 3 years. From then on she deteriorated and within three months she was as bad as ever. On readmission she had signs of tight stenosis but none of incompetence. At operation it was possible to approach the valve via the appendage again. A tight stenosis had recurred (3·5 cm. circumference) and as valvotomy by the usual means was found impossible, both commissures were fully opened by the transventricular route, the final orifice having a circumference of 10 cm. She made a good recovery from her operation but some incompetence followed.

Case 9. A woman, aged 43, had a history of progressive dyspnœa for the last three years. Recently she had become gravely disabled with hæmoptyses and orthopnœa. At operation by Mr. Holmes Sellors she was found to have a soft mobile valve with a very tight stenosis: the lateral commissure was completely divided and the medial one for two-thirds of its length, and afterwards the diastolic murmur had almost disappeared.

After three months a fair result had been achieved, and her ankle œdema had gone. Then she deteriorated and seven months after her operation was as bad as she had ever been and remained so until her readmission four years after her first operation in congestive cardiac failure that responded poorly to treatment. Cardiotomy was undertaken as an emergency. As the appendage had not been amputated at the first operation it was possible to approach the valve the usual way. There was a tight stenosis (3·5 cm. circumference) and slight mitral incompetence, but the valve was still freely mobile. On this occasion a complete split of both commissures was obtained by means of the finger and knife. A fair result was achieved by this operation but she has recently had another attack of congestive cardiac failure.

Case 10. A. A., a woman, aged 46, had had several attacks of pulmonary œdema during the past 18 months. She had moderate disability and gave a history of paroxysmal nocturnal dyspnœa and of orthopnœa. At operation she was found to have a mobile elastic valve but only a fair split was achieved: the medial commissure was completely divided but little impression could be made on the lateral one. The final orifice was about 6 cm. in circumference.

A little improvement was achieved by this operation but it was not maintained. She was readmitted three years later. Her disability was the same as before and her physical signs were unaltered. At operation the valve was approached via the atrial wall, and was found to be soft and mobile with a circumference of 4·5 cm. The medial commissure gave the impression of having completely refused. Again little improvement could be obtained with the finger or the knife. A dilator was therefore passed through the ventricular wall and opened widely. Both commissures were thus completely split, and the final circumference was thought to be 9 cm. There has been considerable objective improvement since this operation.

Case 11. D. D., a woman, aged 38, had a history of occasional hæmoptyses and of recent ascites. Her disability was severe. At operation her appendage was found to be full of clot: this was dissected out and the valve was approached in the usual way. It was found to be mobile and tightly stenosed. The medial commissure was completely divided, but the lateral one was not split beyond the point of tendon insertion.

After the operation she had an excellent result with no disability whatever. This improvement was maintained for two and a half years. Dyspnœa then recurred, and she had several attacks of paroxysmal nocturnal dyspnœa. There was no history to suggest that she had had a recrudescence of rheumatic fever.

She was readmitted three years later with signs of tight mitral stenosis. Her disability was again severe. At operation it was possible to approach the valve by the usual route as the appendage had not been amputated. The mitral orifice was 4 cm. in circumference and the medial commissure was completely refused. Only a moderate increase could be achieved with the finger and knife and the valve was therefore split completely via the ventricle. A minor degree of incompetence was created in the process. Little improvement was achieved at first, but afterwards she was improved.

Case 12. L. J., a woman, aged 39, had a six-year history of increasing dyspnœa, and of occasional ankle œdema. She was moderately disabled (Grade 2) and had a pure mitral stenosis. At operation, she was found to have a mobile mitral valve with a moderate degree of stenosis. The antero-lateral commissure was fully split; the postero-medial one was not divided as it was heavily calcified. A good result was achieved by this operation until three years later, when she had subacute bacterial endocarditis, the infecting organism being *Staphylococcus aureus*. She developed signs of right heart failure and of mitral incompetence, but recovered slowly with penicillin treatment, but after her discharge her exercise tolerance gradually decreased, and she was readmitted a year later with severe disability (Grade 3). She was diagnosed as restenosis. At operation the valve was approached via the atrial wall, and both commissures were found to be firmly fused with an orifice of 3·5 cm. in circumference, but no incompetence. The antero-lateral commissure was easily split with the finger, but the methods of transventricular dilatation had to be used to open the postero-medial one. Grade 1 mitral incompetence was created but the patient made a good recovery and now has a good exercise tolerance.

The first eight cases were examples of false restenosis in that the original division of the commissures was not carried beyond the critical point of tendon insertion on either side in any of them. The last four were examples of true restenosis as in all of them at least one commissure was fully divided. The salient features of these 12 cases are summarized in Table II.

TABLE II

DETAILS OF THE TWELVE CASES REPORTED HERE

Case	Age and sex	First operation	Interval in years	Type of restenosis	Comment and cause of inadequate operation	Second operation		
						Approach	Commissurotomy *	Result
1	40 F	Dil.	2	False	Inexperience	W	A.L.C.	G
2	42 F	Half P.M.C.	4	False	Calcification	W	Both comm.	G
3	40 M	Dil. Half P.M.C.	3	False	,,	W	,, ,,	G
4	39 F	Dil.	1½	False	,,	W	,, ,,	G
5	40 F	Dil.	2	False	Elastic valve	W2	Dil.	P†
6	36 F	Half A.L.C.	2	False	M.I. and calcif.	W	,, ,,	F
7	26 F	Dil.	2½	False	Calcification	W2	,, ,,	G
8	37 F	Dil. Half P.M.C.	3	False	Elastic valve	A	,, ,,	G
9	43 F	Almost complete	4	True	No R.F.	A	Both comm.	F
10	46 F	One comm.	3	True	,,	W	,, ,,	F
11	38 F	One comm.	2½	True	,,	A	,, ,,	G
12	32 F	One comm.	5	True	S.B.E.	W	,, ,,	G

* At all the second operations division of the commissures was with a transventricular dilator except in Cases 1 and 9 when it was with finger and knife.

Cols. 3 and 8. Dil.—dilatation only. One comm.—complete division of one commissure. P.M.C.—posteromedial commissure. A.L.C.—anterolateral commissure.

Col. 6. R.F.—rheumatic fever. S.B.E.—subacute bacterial endocarditis.

Col. 7. W refers to an approach through the atrial wall, W.2 to a second approach via this route, and A to an approach via the appendage.

Col. 9. G—good. F—fair. P—poor. †—died later.

OPERATION FOR RESTENOSIS

In nine of the twelve cases presented here, the approach was made through the atrial wall. The reason for this was that the appendage was removed at the first operation in the hope that the risk of late embolism might be lessened (Belcher and Somerville, 1955). In two of the nine, the valve was reached via the atrial wall at both operations, and in one a third approach has now been made by this route. Although this approach may be more difficult, it carries no added risk unless there is thrombus in the atrium. In these cases, only one ring of purse-string suture was used: the second row recommended by Baden and Therkelsen (1954) was found to be unnecessary. A small incision was made inside this ring and the opening was enlarged by the insertion of the finger. This avoided the risk of cutting the purse string suture. No trouble was met when the suture was tied, and in several cases no further stitch was needed in the atrial wall. In the other three the lumen of the atrium was reached via the appendage in the usual way, as it had not been amputated at the first operation (Table II).

In two of the twelve cases it was possible to divide the commissures in the normal way with finger and knife. In one of these true restenosis had occurred (Case 9); in the other the original valvotomy had been inadequate because of inexperience, and it was more successful on the second occasion (Case 1). In the remaining ten the commissure could not be divided by the normal method. In six of these (Cases 2, 3, 4, 6, 7, and 12) heavy calcification of the valve had prevented adequate splitting at the first operation. In two (Cases 5 and 8) the elasticity of the valve accounted for the poor split, and in the two where true restenosis had occurred (Cases 10 and 11) division of the commissure which was not cut at the first operation was again found to be impossible.

To achieve a complete division of the commissures in these ten patients the alternative method of transventricular dilatation described by Logan was used. When the valve had been explored a

small incision was made in the wall of the left ventricle near the apex. A sound was passed into the lumen; this was withdrawn and the dilator was introduced; this was passed on until it could be felt engaging the orifice and it was then opened until the blades were 4 cm. apart: the guard was then removed and the blades were further opened to 5 cm. The dilator was then removed and the wound in the ventricle was easily controlled with a few sutures. In all save one case complete separation of both commissures was thus achieved.

TABLE III

DETAILS OF THE SECOND OPERATIONS REPORTED BY OTHERS

Author	1st operation	Interval in years	Findings	2nd operation	Result
Morino	A.L.C.	3	Tight stenosis	Both comm.	G
Keyes	A.L.C.	2	Tight stenosis	Almost complete	G
Glenn	A.L.C.	2	Readherence A.L.C.	Both comm.	Died
Santy	A.L.C.	3	,,	One comm.	F
Baden	One comm.	3	Tight stenosis	Both comm.	?
Bailey	Dil	6	Tight stenosis	?	?
Baronofsky ..	M.I.	2	Tight stenosis	Both comm.	G
,,	M.I.	1	Tight stenosis	One comm.	Died
,,	Thrombosed atrium	1	Tight stenosis	Both comm.	G
,,	Dil	2½	Restenosis	One comm.	G
,,	?	6	?	One comm.	

The abbreviations are the same as those in Table II.

RESULTS

There was no operative mortality, but a massive cerebral embolus caused one late death (Case 5). Of the others, eight have been classed as good and three as fair. Minor mitral imcompetence was created in Cases 6, 9, and 12 and considerably increased in Case 7. In only eight of the twelve has a sufficient time elapsed to assess the extent of improvement. These results are perhaps not as good as might have been expected from the efficacy of the division of the commissures, all of which were good, but it is possible that further improvement will occur.

DISCUSSION

Eleven of the twelve cases reported here are derived from a series of 240 operations, 120 of which were performed more than two years ago. They were classed as good where both commissures were fully opened, as fair to good where the split was almost complete; as fair where only one commissure was opened or where both were partially split, and as poor where neither commissure was divided beyond the critical point of tendon insertion.

The efficacy of the split had a close relationship to the incidence of restenosis. There were 186 patients in the first two groups; if restenosis had occurred in any of these it would have been true restenosis, but none of them has so far required a second operation. Of the 43 patients in whom the split was classified as fair, five have so far been operated on for a second time; two of these were regarded as true restenosis. Of the eleven in whom the split was regarded as poor, one died at operation, one has died since, and six have been operated upon for a second time: these were all examples of false restenosis.

These findings suggest that many patients who have a poor division of the commissures will almost certainly require a second operation, whereas those who have complete or almost complete division have only a small risk of restenosis.

These findings also re-emphasize the importance of adequate division of the commissures at the first operation, for it is probable that at least four of the twelve patients presented here would

not have required a second operation if the transventricular dilator had been used on the first occasion when the knife and finger method failed.

The results in this series has shown that the second operation has been well worth while. The reported cases where a second operation has been done are summarized in Table III. As will be seen there are eleven cases in all; of these two died, but in the remainder the extent of improvement again followed the extent of the division closely.

It therefore seems that there is every justification for a second operation when restenosis is diagnosed, particularly in those patients in whom the original operation is known to have been inadequate. If false restenosis can be eliminated by a good division of the commissures at the first operation, restenosis will prove to be uncommon.

Summary

Two varieties of restenosis have been described; true restenosis, which occurs after one or both commissures have been fully split, and false restenosis where the original operation was inadequate. True restenosis may be rheumatic in origin; false restenosis may be inevitable after any poor commissurotomy.

The reported cases of restenosis have been reviewed, and twelve patients who have been operated upon for a second time are described. Eight had false restenosis and four had true restenosis.

There was no mortality in the series. The results have been satisfactory. In ten the second division of the commissures was performed by the transventricular technique of Logan. In all save three the approach was made through the atrial wall.

My thanks are due to Dr. D. E. Bedford and to Dr. K. Shirley Smith, under whose care some of these cases were admitted.

References

Baden, H., and Therkelsen, F. (1954). *Thorax*, **9**, 340.
Bailey, C. P. (1955). *Surgery of the Heart*. Kimpton.
Baker, C., Brock, R. C., and Campbell, M. (1955). *Brit. med. J.*, **2**, 983.
Baronofsky, I. D., Borden, C., Smith, R. F., and Sparafka, J. L. (1955). *Ann. Surg.*, **142**, 32.
Belcher, J. R., and Somerville, W. (1955). *Lancet*, **2**, 1000.
Brock, R. C. (1952). *Brit. Heart J.*, **14**, 489.
—— (1956). *Ann. Roy. Coll. Surg.*, **19**, 1.
Canigia, A. (1955). *Acta. Cardiol. (Brux.)*, **10**, 67.
Cooley, D. A. (1951). *Angiology*, **2**, 591.
Dussailant, G. (1954). *Rev. Med. Chile*, **82**, 92.
Donzelot, E., Dubost, C., de Balzac, R. H., Métianu, C., and Guillemot, R. (1953). *Arch. Mal. Cœur*, **46**, 300.
Glenn, F., and Dineen, P. (1956). *Ann. Surg.*, **143**, 405.
Glover, R. P., Davilla, J. C., O'Neill, J. E., and Janton, O. H. (1955). *Circulation*, **11**, 1.
—— (1955). *Trans. Amer. Coll. Card.*, **5**, 209.
Goodwin, J. F., Hunter, J. D., Cleland, W. P., Davies, L. G., and Steiner, R. E. (1955). *Brit. med. J.*, **2**, 573.
Jordan, P., and Hellems, A. K. (1952). *Surg. Gyn. Obst.*, **95**, 689.
Keyes, J. W., and Lam, C. R. (1954). *J. Amer. med. Ass.*, **155**, 247.
Lam, C. R. (1955). *Cardiovascular Surgery*. Saunders.
Logan, A. (1955). Personal communication.
McKusick, V. A. (1955). *Arch. intern. Med.*, **95**, 557.
Morino, F. (1955). *Minerva Med. Tor.*, **46**, 1033.
Muller, W. H. (1952). *Surgery*, **31**, 602.
Santy, P., Froment, R., Gallavardin, L., Tolot, F. (1954). *Arch. Mal. Cœur*, **47**, 7.
Sellors, T. H., Bedford, D. E., and Somerville, W. (1953). *Brit. med. J.*, **2**, 1059.
Turner, H. W. D., and Fraser, H. R. L. (1956). *Lancet*, **2**, 525.
Wood, P. (1954). *Brit. med. J.*, **1**, 1113.
—— (1956). Personal communication.

CORONARY HEART DISEASE IN THE PRESENCE OF PULMONARY DISEASE

BY

ARTHUR J. THOMAS

From Llandough Hospital, United Cardiff Hospitals

Received May 25, 1957

In the course of our studies of pulmonary heart disease we have been impressed by the frequent co-existence of coronary heart disease noted at necropsy but less frequently recognized during life. Pulmonary disease even before the advent of heart failure, was readily recognized by its symptoms of dyspnœa and cough and by its radiological signs. The co-existent coronary heart disease was often symptomless, or if pain was present it required differentiating from pleuropulmonary pain. Radiology was able to help only by showing an enlarged left ventricle in some of the cases. It seemed that electrocardiography would be the best examination to reveal the presence of the coronary heart disease with pulmonary disease, but consideration of the electrocardiographic signs of both conditions immediately revealed difficulties of interpretation.

Such difficulties are exemplified in Fig. 1, 2, and 3. The patient whose electrocardiogram is shown in Fig. 1 had pure pulmonary heart disease which, in the space of three years, had produced

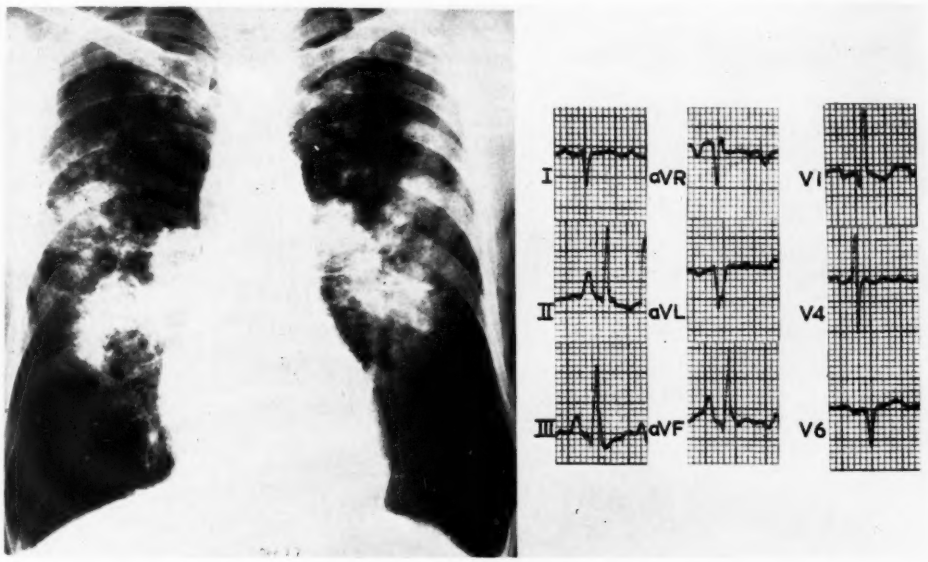


FIG. 1.—Man, aged 50 years. Pure pulmonary heart disease with its electrocardiographic pattern developing between 1952 and 1954. Width of QRS=0·08 sec.

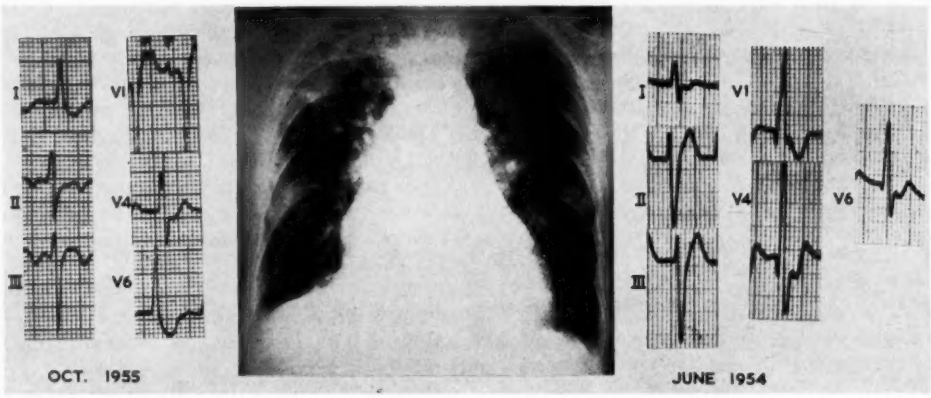


FIG. 2.—Man, aged 55 years, with coalworkers' pneumoconiosis and calcific aortic stenosis. The electrocardiogram changed on three occasions to a pattern of right bundle-branch block; QRS of width 0·12 sec.

right ventricular hypertrophy. In Fig. 2 are shown the electrocardiograms of a patient with cardiac pain on effort, an aortic systolic murmur, and a changing record, which at times suggested right ventricular hypertrophy or right bundle-branch block. This case was thought at one time to have coronary heart disease but at necropsy the coronary arteries were quite healthy, the left ventricular muscle was greatly hypertrophied, and the aortic valve calcified and stenosed. In the third example, depicted in Fig. 3, there was well-recognized pulmonary heart disease but also a systolic murmur, moderate hypertension, and a rather sudden change in the electrocardiogram between November, 1954, and March, 1955. At necropsy in December, 1955, the heart was 397 g. in weight with the left ventricle weighing 164 g. and the right ventricle weighing 110 g. There was a small right coronary artery with severe atheroma, occlusion of the anterior descending branch

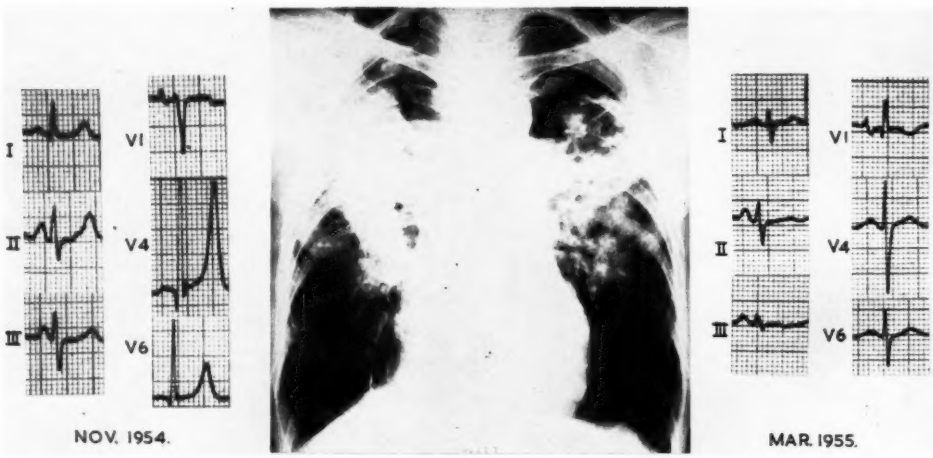


FIG. 3.—Man, aged 62 years, with coalworkers' pneumoconiosis and coronary heart disease. The electrocardiogram changed between November, 1954 and March, 1955 to a pattern of right ventricular hypertrophy or incomplete right bundle-branch block; QRS of width 0·09 sec.

of the left coronary artery with infarction of the lower half of the interventricular septum. The change in the electrocardiogram was thought to result from the myocardial injury.

Material and Method of Study

These difficulties led us to carry out a correlation of the clinical features and the findings at necropsy in 69 patients with severe pulmonary disease. The cases selected for study have been miners or ex-miners because, by courtesy of the Pneumoconiosis Research Unit (M.R.C.), it has been possible to follow these in detail over a period of years. It is important to realize that the pulmonary disease was not only pneumoconiosis but often bronchitis and emphysema of the type seen also in non-industrial pulmonary disease. The other advantage of this clinical material was that long-term study of patients with pure pulmonary heart disease (Thomas, 1948 and 1951) had made us familiar with the variations of the symptoms, signs, and electrocardiograms in such cases.

Coronary heart disease has been regarded as present when there was evidence of myocardial damage macroscopically or on histological examination, with reduction by a third or more of the lumen of a major vessel; it has been considered present also without detectable myocardial damage in the presence of occlusion, recanalization, or extreme narrowing of a major coronary vessel.

A study of 69 patients has been made. Of these, 32 had clinical and necropsy evidence of coronary heart disease; 26 had doubtful evidence of coronary heart disease which was not confirmed at necropsy but other heart disease was revealed; the remaining 11 patients had significant coronary artery disease at necropsy that had not been diagnosed during life.

Of the 32 patients with proven coronary heart disease the average age at death was 62 years (46–74 years). They were divisible into two groups; 14 cases with frank myocardial infarction and 18 with severe coronary artery disease without frank infarction. The average heart weight of those with myocardial infarction was 455 g. (340–700 g.), while those with severe coronary artery disease only it was 302 g. (220–400 g.). The difference in weight was contributed by the left ventricle. The heavier hearts of those with myocardial infarction is in accord with the findings of Harrison and Wood (1949). In some of the cases there was right ventricular hypertrophy, but this applied equally to both groups and did not alter the difference.

The Clinical Signs

It is important to note that cardiac pain was not identified in five patients with myocardial infarction. There are several reasons for this; recurrent pleuro-pulmonary pain is frequent and it is not always easy to distinguish cardiac pain in a retrospective history; also, painless myocardial infarction does occur in syndromes of this kind. In those with coronary artery disease without infarction, five had cardiac pain on effort, but pulmonary disability restricted effort in some of the other cases and so masked any possible cardiac pain on effort.

Hypertension was not very common. If there was gross pulmonary fibrosis, the blood pressure tended to drop and in the last year or two of life might not be above 160/100 mm. Hg, even if it had been higher than this in earlier years. Whether the fall was due to loss of weight, to enforced rest, or to the cutting down of pulmonary blood flow was not clear.

Electrocardiography in the Differential Diagnosis

The electrocardiographic signs of classical myocardial infarction need no comment. The presentation of the right bundle-branch block pattern caused difficulty but in this series it occurred more commonly with coronary heart disease than with pulmonary heart disease alone, in the proportion of five to one (Fig. 4). The numbers are small but they suggest that the identification of the cause of the right bundle-branch block pattern is important. In two instances the presence of abnormal Q waves in lead III and S–T depression over the left ventricle suggested coronary artery disease with right bundle-branch block. There was difficulty with a high R wave in V1 without widening of the complex beyond 0·09 sec. as this could be due to right ventricular hypertrophy or incomplete right bundle-branch block. This finding develops slowly when due to right ventricular

hypertrophy but suddenly in coronary heart disease, and it was on the score of this difference that the lesion shown cardiographically in Fig. 3 was thought to have arisen from coronary heart disease. Furthermore, coronary heart disease may be suspected if there is right bundle-branch block with no other evidence of right ventricular hypertrophy and no alternative explanation of its presence.

In this series the lesser electrocardiographic signs of myocardial injury (Evans and McRae, 1952) have been found of great value and the form of the S–T segment has been as important as its actual depression (Holzmann, 1952). Left axis deviation with S–T depression in lead I, a qR complex with T inversion in aVL, a trough or deep depression of S–T segment and a low, blunt or flat T wave in V6 were present with coronary heart disease and these signs were not seen in pure pulmonary disease (Fig. 5 and 6). Right axis deviation with S–T depression or T inversion in

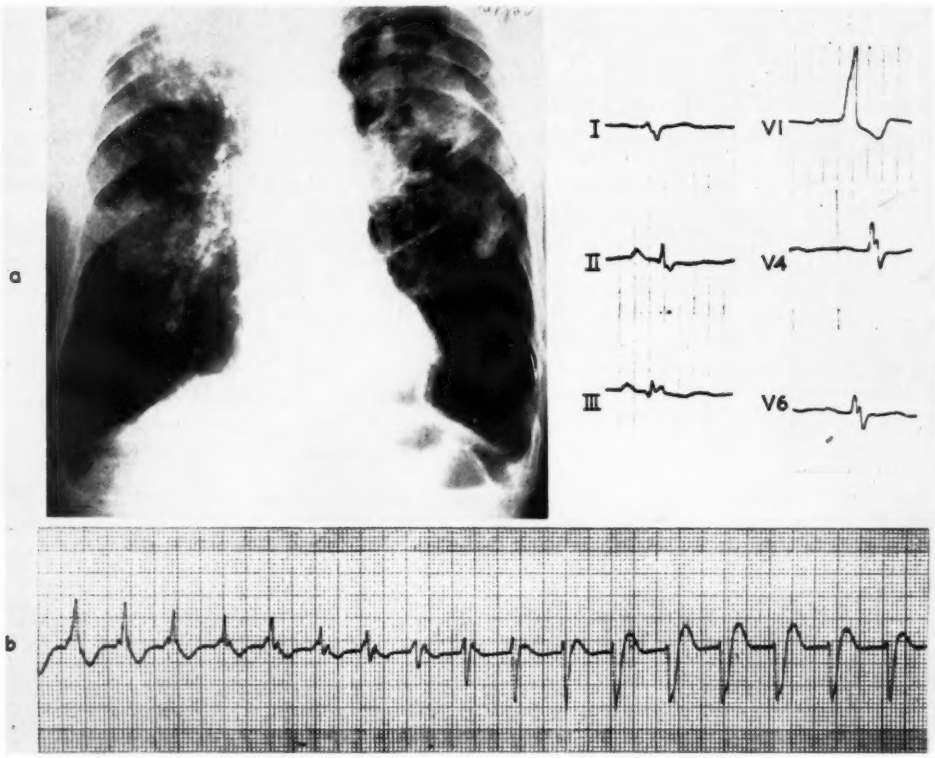


FIG. 4.—(a) Man, aged 62 years, with pulmonary disease and coronary heart disease. Electrocardiograph of right bundle-branch block (QRS of 0·12 sec.). The heart weighed 500 g., with the right ventricle 7 mm. and the left ventricle 16 mm. in thickness.

(b) Man, aged 61 years, with bronchitis and emphysema, mitral incompetence, myocardial fibrosis, and coronary artery disease. Lead V1, showing pattern of changing intraventricular conduction. Heart weight 493 g., the right ventricle 140 g. and the left ventricle 208 g.

leads III, aVF, and V6 was more difficult to interpret but the presence of S–T changes of trough or plane depression in V6 was usually associated with coronary heart disease and was not present in pure pulmonary heart disease unless there was extreme rotation or distortion. The type of T inversion in lead III was abnormal in some cases with the curved S–T segment and deep T wave

inversion suggesting myocardial injury (Fig. 6). Auricular fibrillation was so extremely rare in pure pulmonary heart disease that it was regarded always as indicative of other heart disease, and in four patients of this series it was present with combined pulmonary and coronary heart disease.

In general, the pulmonary disease tends to produce an electrocardiogram denoting a vertical heart and aVL is then of QS or rS type with T wave inversion. When the aVL is of qR pattern the S–T segment is isoelectric and the T upright in the normal or pulmonary case. Occasionally, an electrocardiogram has shown a qR complex in aVL with a curved S–T segment convex upwards to an inverted T wave. On both occasions in this series this form of aVL has accompanied coronary heart disease and has not been present in the pure pulmonary heart disease group. A further series will be required to assess aVL but it would seem that a qR complex with S–T curving to T inversion is an abnormality not associated with pulmonary heart disease but with concomitant coronary heart disease or left ventricular hypertrophy.

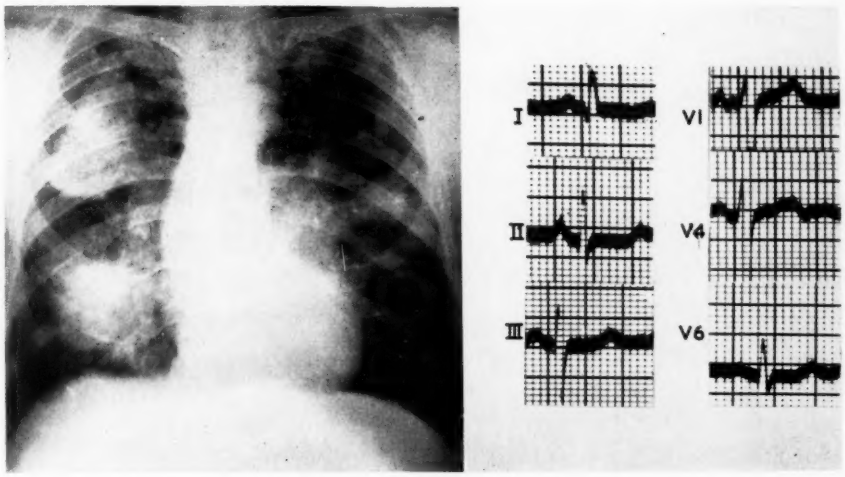


FIG. 5.—Man, aged 65 years, with coalworkers' pneumoconiosis and coronary heart disease. The heart weighed 340 g. with the right ventricle 6 mm. and the left ventricle 15 mm. in thickness.

The simple changes of left axis deviation and blunt T waves from left ventricular leads cannot be taken as evidence of coronary heart disease as they may well be the result of left ventricular preponderance or hypertrophy, but they are quite unusual in fully developed pulmonary heart disease and may be regarded as indicators of some other heart disease affecting the left ventricle.

In many of these patients there were other clinical signs to support the diagnosis. There was cardiac pain in 14 cases; there was the helpful sign of left ventricular enlargement that could not be explained on other clinical grounds; and there were signs of atherosclerosis of the aorta and other vessels. Final assessment of the presence of coronary heart disease with pulmonary disease required the consideration of all these factors, together with the exclusion, if possible, of other causes of left ventricular hypertrophy. The electrocardiogram was of proven value in making the diagnosis.

THE DIFFERENTIAL DIAGNOSIS OF OTHER HEART DISEASES

There were 26 patients suspected at some time, on clinical or electrocardiographic grounds, of having coronary heart disease but in whom this was not found at necropsy. These are worthy of analysis because of the other heart diseases present. In six of them the electrocardiogram was

that of pure pulmonary heart disease, but doubt arose through clinical findings such as thoracic pain; necropsy revealed no heart disease. Two others were suspect because of the altered S–T segments and flat or inverted T waves in V4, but this sign was clearly compatible with pure pulmonary heart disease if the T wave was upright in V6.

The other 18, in all of whom the doubtful sign was in the electrocardiogram, were distributed as follows:

Myocardial fibrosis of unknown origin	4
Hypertensive heart disease	4
Pericarditis	2 (*continued*)

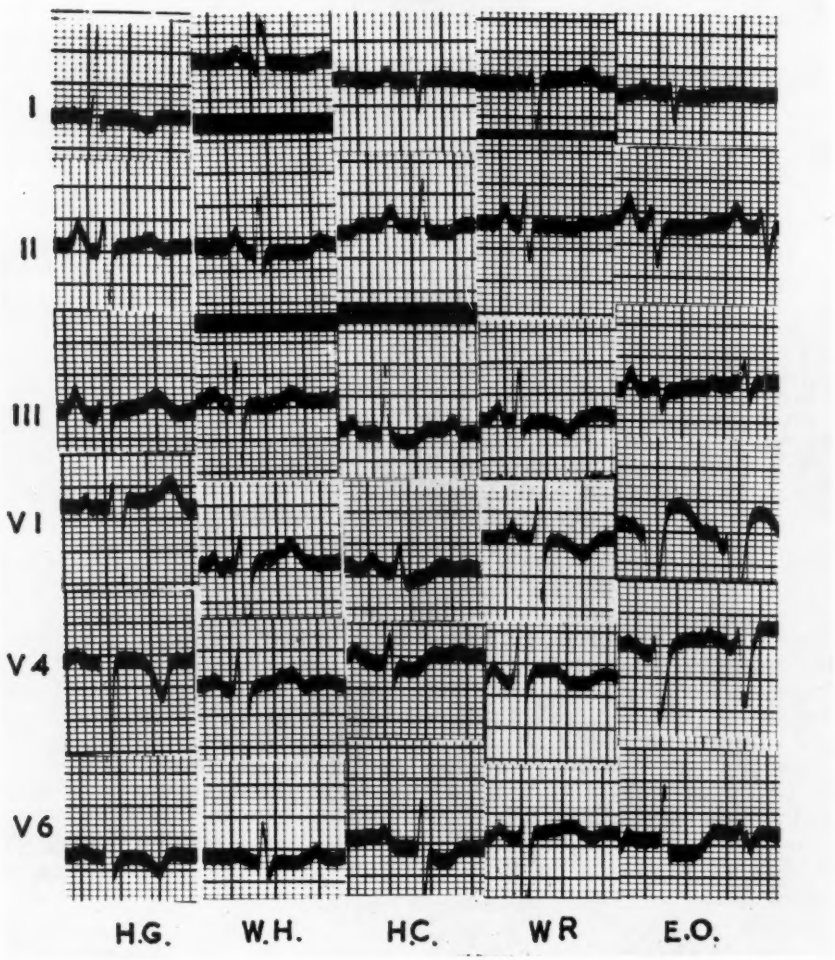


FIG. 6.—Five examples of electrocardiograms in proven pulmonary disease and coronary heart disease. The departures from the usual pulmonary heart pattern are considered to be due to the effect of coronary heart disease.

Paroxysmal tachycardia	2
Heart block	2 (1 of which was due to digitalis)
Right bundle-branch block	1
Flat T waves in the electrocardiogram	3

On retrospective scrutiny the cases of myocardial fibrosis and those of heart block would still be suspected of coronary heart disease, because of the form of the electrocardiogram or the radiological prominence of the left ventricle. Transient prolongation of the P–R interval has been seen in pure pulmonary heart disease and is not regarded as due to myocardial injury. The clinical findings have helped to establish the presence of hypertensive heart disease, aortic stenosis, and pericarditis, but electrocardiography alone could be confusing when these conditions co-existed with severe pulmonary disease (Fig. 2). Difficulty arises from the occasional appearance of flat T waves in the electrocardiogram of pure pulmonary disease, and this is not fully explained yet. This group of cases indicates the difficulty that may arise in the recognition of coronary heart disease when other heart diseases may also be present.

The Non-recognition of Coronary Artery Disease

There were 11 patients who at necropsy had significant coronary artery disease that had not been discovered during life. In three of them there was marked right ventricular hypertrophy and this appeared on the electrocardiogram, but the leads recorded did not reveal the left ventricular pattern properly, although they included præcordial leads to V6. In two other cases it was likely that the electrocardiograms were taken before the final changes due to coronary heart disease had appeared. One other patient had been accepted as having hypertensive heart disease. The five remaining had severe coronary artery disease but they had not produced any recognizable clinical picture or electrocardiographic abnormality when death occurred from other causes. The average heart weight in this group of 11 cases was 323 g. (220–397 g.), and was similar to the first group recognized as having coronary artery disease without frank myocardial infarction.

The findings in these 11 patients suggest that detection of coronary heart disease with pulmonary disease requires repeated electrocardiograms, especially in episodes of pulmonary infection; the leads recorded must include those derived from the left ventricle which may be situated more posteriorly than usual. Even so, severe coronary artery disease is present occasionally without affecting the myocardium and so is clinically silent.

Discussion

As chronic pulmonary disease occurs so often in middle age or later, it coincides with the period of high prevalence of coronary artery disease. Both of these diseases affect the heart and, as suggested by Drake (1951), they may exert an unfavourable influence one on the other. The diagnosis may not be made completely, and the disease most likely to pass unnoticed clinically is that of the coronary arteries. There is no suggestion as yet that chronic pulmonary disease predisposes to a higher prevalence of coronary disease, but both may be unduly prevalent in the population studied in this work.

The detection of coronary heart disease is made easier once the suspicion of its presence has arisen. The finding of cardiac pain is of great value, but because pleuro-pulmonary pain is common in chronic respiratory disease, attention has to be paid to all the criteria for identifying cardiac pain. These have been reviewed by Master *et al.* (1954).

In the study of the effects of pulmonary disease on the heart, I have been impressed by the rarity of left ventricular enlargement or hypertrophy in pure pulmonary heart disease. Thus, if it is found, another explanation of the increased size of the left ventricle must be sought. In this work, the heavier left ventricle has been associated with myocardial infarction in a number of cases.

Aortic stenosis, of mild degree, is not uncommon in the later age groups and appears at times in association with severe pulmonary disease. Two things have happened: aortic stenosis has

mimicked myocardial infarction and also, in an earlier series, a case of proven calcific aortic stenosis with advanced pulmonary disease eventually died of coronary occlusion. It is clearly important to assess the heart from the standpoint of a possible aortic stenosis before identifying coronary heart disease.

The other cause of left ventricular enlargement that has to be analysed is hypertension. This analysis is rendered difficult because severe anoxia in the pulmonary disease elevates the blood pressure to considerable heights for short periods. This hypertension, however, does not affect the left ventricle or the left ventricular pattern of the electrocardiogram. On the other hand, patients with severe pulmonary fibrosis and known systemic hypertension have lost the high blood pressure readings in the last year of their illness, but signs of the hypertrophied left ventricle have remained, particularly in the electrocardiogram.

The finding of four examples of myocardial fibrosis with left ventricular enlargement and no detectable cause is surprising and demands further investigation.

The electrocardiogram has been of the greatest help in the diagnosis of coronary heart disease in the presence of pulmonary disease. It has revealed unsuspected coronary heart disease and has explained the unusual behaviour in some cases of pulmonary heart failure. However, the pattern of right ventricular hypertrophy can resemble that of myocardial infarction and cause difficulty (Myers, 1950). The electrocardiogram has recorded myocardial injury or ischæmia in some form and it is not surprising that the occasional case of myocardial fibrosis of unknown origin appears with the diagnosis of coronary heart disease. Left ventricular hypertrophy needs to be differentiated from coronary heart disease in the electrocardiogram but in many instances this has been possible. The changes in various forms of heart block have been confusing, but the interesting finding is that the right bundle-branch block pattern has appeared more frequently because of coronary heart disease than of pure pulmonary disease.

Further application of the electrocardiogram, particularly with detection of the lesser changes of myocardial injury (Evans and McRae, 1952), should prove of great interest in cases of pulmonary disease. The exercise tests have not proved helpful when there is severe pulmonary disease because the dyspnœic patient is already applying the equivalent of an exercise test to himself, but if the pulmonary disease is slight then the exercise test has taken its proper place. The ballistocardiographic pattern was not helpful as the complexes were greatly reduced in amplitude and changed in form by the pulmonary disease and by the coronary heart disease without there being distinguishing features.

This work has drawn our attention to the need for detailed analysis of all the findings in chronic pulmonary disease to exclude co-existent heart disease, particularly coronary heart disease.

Summary

A review of the clinical features, electrocardiographic patterns, and necropsy findings in 69 cases of severe pulmonary disease shows the problem of the diagnosis of co-existing coronary heart disease. In 32 coal workers with severe pulmonary disease and necropsy proof of coronary heart disease the diagnosis could be made from clinical and electrocardiographic signs. Cardiac pain required differentiation from pleuro-pulmonary pain but was not always present. Myocardial infarction was accompanied by an increase in size and weight of the left ventricle. Five groups of electrocardiographic patterns were selected as indicative of coronary heart disease in the presence of pulmonary disease, but certain difficulties were recognized. These groups were (a) the electrocardiogram of frank myocardial infarction; (b) the pattern of bundle-branch block when this was not considered due to right ventricular hypertrophy or when signs were seen of myocardial infarction with the bundle-branch block; (c) left axis deviation with S–T changes and T wave inversion in left ventricular leads; (d) right axis deviation with the presence of significant S–T depression in left ventricular leads and occasionally in these cases a qR in aVL with T wave inversion; and (e) the presence of auricular fibrillation when other heart disease was not present to explain it. Difficulties arose in the recognition of other causes of left ventricular enlargement, such as aortic stenosis or

myocardial fibrosis of unknown origin, and in the identification of the causes of various degrees of heart block. It is clear that with serial electrocardiograms by paying attention to the interpretation of the lesser electrocardiographic signs of myocardial injury, the accuracy of diagnosis of coronary heart disease can be greatly increased even in the presence of severe pulmonary disease. Some of the errors that occur would seem to be at the present moment unavoidable, but require further study.

Some of our patients had coronary artery disease that was clinically silent and in these cases a diagnosis before necropsy could not be expected. It is evident that the presence of coronary heart disease will generally modify the clinical picture of pulmonary heart disease; it may account in part for unexpected cardiac findings; or it may hasten the end. It is therefore worth while investigating critically for coronary heart disease all patients with chronic pulmonary disease.

I am greatly indebted to Dr. J. C. Gilson, Director of the Pneumoconiosis Research Unit (M.R.C.), for access to the clinical material; to Professor J. Gough and his staff, Department of Pathology, Welsh National School of Medicine, and Dr. J. Rivers for the necropsy studies; and to Mr. L. Williams for the illustrations.

REFERENCES

Drake, E. H. (1951). *Ann. intern. Med.*, **35**, 600.
Evans, W., and McRae, C. (1952). *Brit. Heart J.*, **13**, 457.
Harrison, C. V., and Wood, P. H. (1949). *Brit. Heart J.*, **11**, 205.
Holzmann, M. (1952). *Clinical Electrocardiography*. Translated by Robertson, D., Staples Press, London.
Master, A. M., Jaffe, H. L., and Pordy, L. (1954). *Ann. intern. Med.*, **41**, 315.
Myers, G. B. (1950). *Circulation*, **1**, 860.
Thomas, A. J. (1948). *Brit. Heart J.*, **10**, 282.
—— (1951). *Brit. Heart J.*, **13**, 1.

PATENCY OF THE DUCTUS ARTERIOSUS IN THE NEWBORN CALF AND FOAL

BY

E. C. AMOROSO, G. S. DAWES, AND JOAN C. MOTT

From the Nuffield Institute for Medical Research, University of Oxford

Received June 22, 1957

In the lamb, the ductus arteriosus does not close immediately after birth, but the direction of blood flow through it reverses. In the newborn lamb, therefore, blood normally flows from the aorta, through the ductus arteriosus, to the lungs (Born *et al.*, 1955*c*; Dawes *et al.*, 1955 *a* and *b*). Observations in newborn puppies (Handler, 1956) and babies (James and Rowe, 1957; Adams and Lind, 1957) indicate that in these species the course of the circulation is similar to that in newborn lambs. The present paper describes experiments that show the same train of events in two further species, the newborn calf and foal.

METHODS

One foal and three calves were examined in the field by direct auscultation and by phonocardiography. Two further foals and three calves were brought to the laboratory within six hours of birth, and phonocardiographic records were made before light anæsthesia was induced with intravenous sodium pentobarbitone. Two of the calves developed laryngeal spasm after the injection and a tracheal cannula was therefore inserted as soon as possible. The methods used were similar to those described previously (Dawes *et al.*, 1955 *a* and *b*). Artificial positive pressure ventilation was provided by a Starling Ideal pump and access to the ductus arteriosus was obtained by removing the third and fourth ribs on the left side. Systemic arterial blood pressure was recorded from the descending aorta or from a carotid, femoral, or tarsal artery and pulmonary arterial pressure from a branch supplying the apex of the left lung. Blood samples were withdrawn simultaneously from the right ventricle (by direct puncture) and from catheters in the systemic and pulmonary arteries. The blood samples were analysed for their oxygen content and capacity as described previously (Born *et al.*, 1955*a*).

RESULTS

Cardiac Murmurs in Unanæsthetized Newborn Calves and Foals. Six calves were first examined seven minutes to four hours after birth. All exhibited a loud continuous murmur over the ductus arteriosus (Fig. 1b). This murmur had both a cardiac and respiratory variation. It was best heard in the interspace between the third and fourth ribs on the left side, well up in the left axilla. In order to apply the stethoscope bell effectively, it was found desirable to pull the left forelimb gently cephalad. The murmur radiated ventrally for as much as 6 cm., along a narrow band between the third and fourth ribs. It was loudest within the first hour or so after birth and, in three calves, was no longer heard twelve hours later.

In some of the calves another murmur was also present, though for a shorter period of time. This was a presystolic murmur, heard at the apex and along the left side of the sternum (Fig. 1a), which could have been due to rapid flow through the mitral valve.

Three foals were also examined 7 to 7½ hours after birth, and all had a continuous loud murmur over the ductus arteriosus, localized to the same rib interspace, and very similar to that heard in calves (Fig. 2b).

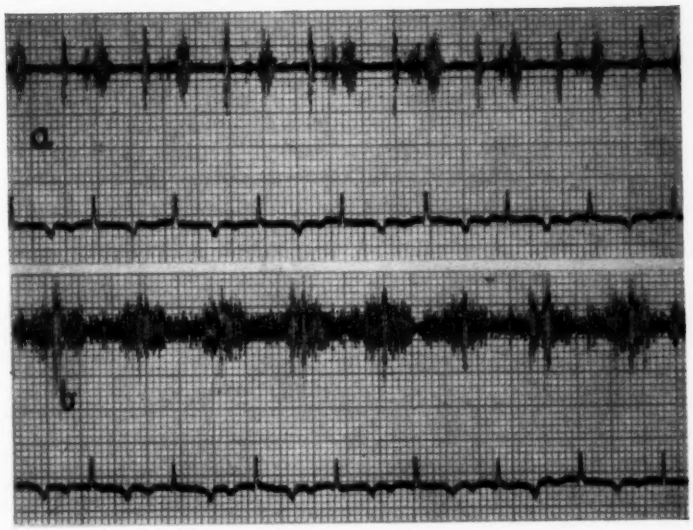


FIG. 1.—Calf, 4½ hours old, unanæsthetized. Records of phonocardiograph (above) and electrocardiograph (below). There is a presystolic murmur at the apex (a) and a loud continuous murmur over the ductus arteriosus (b).

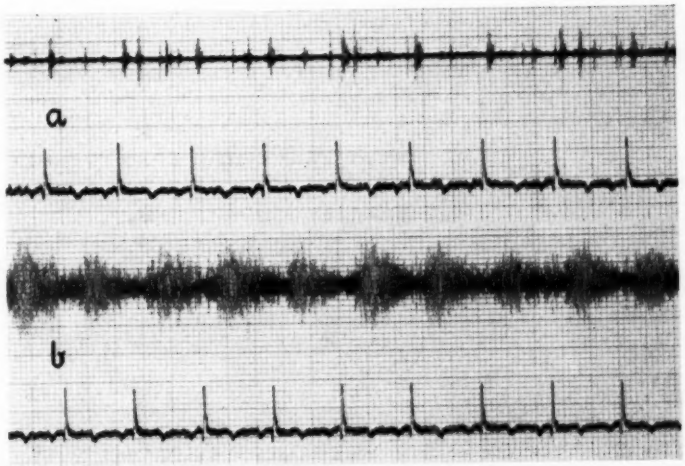


FIG. 2.—Foal, 7 hours old, unanæsthetized. Records of phonocardiograph (above) and electrocardiograph (below). There was no evidence of a murmur at the apex (a), but a loud continuous murmur was heard over the ductus arteriosus (b).

Anæsthetized Calves and Foals. The murmur heard between the third and fourth ribs on the left side of the chest persisted after the animals were lightly anæsthetized. When the chest was opened at this point the ductus arteriosus was found to lie immediately within the chest wall and did not give the impression of being greatly narrowed. The murmur sounded louder when the stethoscope bell was applied directly to the wall of the ductus; it radiated towards the pulmonary trunk, and was sometimes accompanied by a palpable thrill.

The ductus arteriosus was occluded for brief periods in three calves and two foals. This manœuvre invariably caused an increase in systemic arterial pressure and a fall of pulmonary arterial pressure (Fig. 3). The murmur and thrill from the ductus also disappeared on occlusion of the vessel (Fig. 4). These observations led to the conclusion that in the calf and foal, as in the lamb, blood flow persists through the ductus arteriosus from the aorta to the pulmonary trunk for some

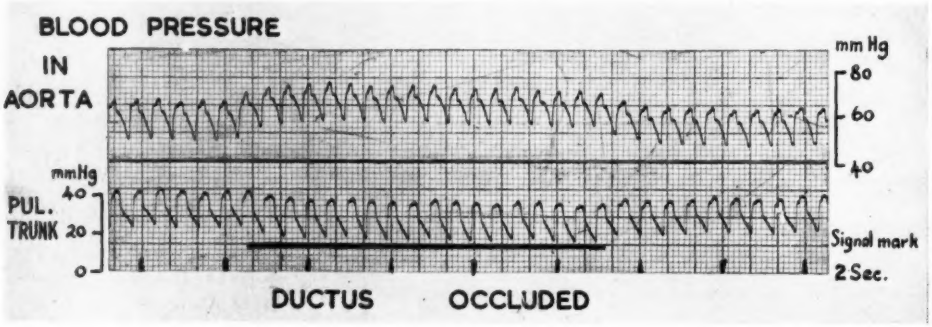


FIG. 3.—Calf, 6 hours old, pentobarbitone anæsthesia. Condenser manometer records of aortic pressure (above) and pulmonary trunk pressure (below). The ductus arteriosus was occluded during the signal mark. Time signal 2 seconds.

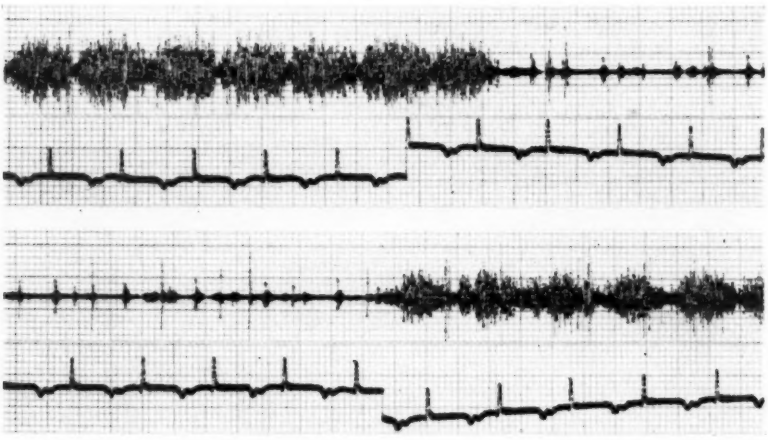


FIG. 4.—Calf, 5½ hours old, pentobarbitone anæsthesia. Phonocardiograph record from junction of ductus arteriosus and pulmonary trunk (above) and electrocardiogram (below). The two records are consecutive. The ductus arteriosus was occluded and released at the abrupt deflections (=1 mv.) in the electrocardiographic record.

hours after birth. This conclusion was confirmed by the analysis of blood samples taken simultaneously from the right ventricle, the pulmonary artery, and a systemic artery. Table I shows that some systemic blood always reached the pulmonary artery.

TABLE I

PERCENTAGE OXYGEN SATURATION OF BLOOD IN NEWBORN CALVES AND FOALS

	Age (hours)	Systemic artery	Pulmonary artery	Right ventricle	Percentage of aortic blood in pulmonary artery
Calf 2	8½	93·5 97	81 81	78·5 78	17 16
Calf 4	6	99·5 97	86·5 84	83 79·5	21 26
Calf 5	6	97 93	84 74	79 69	28 21
Foal 2	9½	94 94	63 63	61 62	6 3
Foal 3	8½	75 96	44 55	35 49	23 12

DISCUSSION

In the lamb, adequate ventilation of the lungs at birth so decreases the pulmonary vascular resistance as to cause the pulmonary arterial pressure to fall below the systemic pressure. The consequence is that blood flow through the ductus arteriosus reverses from the fœtal (pulmonary trunk to aorta) to the neonatal (aorta to pulmonary trunk) direction (Born *et al.*, 1955*c*). In addition, if the velocity of blood flow is sufficient, a continuous machinery murmur may be detected on auscultation. While the presence of such a murmur is, by itself, indicative of a patent ductus arteriosus, its absence does not necessarily imply that the ductus is closed (Dawes *et al.*, 1955*a*). This type of murmur was readily detected in calves and foals as described in this paper, though even in these large animals the area over which the murmur was heard was not extensive.

The existence of a continuous murmur indicated patency of the ductus in the newborn calf and foal, and suggested that the direction of blood flow was from aorta to pulmonary artery, since in the lamb the murmur due to blood flow in the opposite direction is systolic in character (Dawes *et al.*, 1955*a*). Direct evidence as to the direction of blood flow was obtained by observation of the effect of occlusion of the ductus on the systemic and pulmonary arterial pressures. When the blood was prevented from flowing through the ductus, the systemic pressure rose and the pulmonary arterial pressure fell. Moreover, the blood in the pulmonary artery contained more oxygen than that in the right ventricle, and the aortic blood contributed up to a quarter of the pulmonary blood flow. The course of the blood flow through the ductus arteriosus of calves and foals shortly after birth is therefore very similar to that seen in lambs. The proportion of pulmonary blood flow coming from the aorta in calves and foals was lower (3–28%) than in lambs (23–57%) (Dawes *et al.*, 1955*b*), but the calves and foals were several hours old, whereas the lambs' lungs had been ventilated for less than an hour.

James and Rowe (1957) and Adams and Lind (1957) have also found, by passing catheters, that the blood in the pulmonary artery of a newborn baby contains more oxygen than that in the right ventricle. On the other hand Eldridge *et al.* (1955) found more oxygen in samples of finger blood than of heel blood in young babies. While this observation is consistent with a patent ductus, it

implies that blood is flowing through the ductus from pulmonary trunk to aorta. This could happen if the sampling procedure caused, indirectly, an increase of intrathoracic pressure and thereby reversed the normal direction of blood flow.

Angiographic records have also indicated that in both the newborn lamb and the puppy the ductus arteriosus is still open shortly after birth. Although contrast medium could be made to pass either way through the puppy's ductus, the pulmonary arterial pressure was less than the aortic, so that the direction of blood flow must normally be towards the lungs (Handler, 1956).

The murmur associated with the patent ductus of the newborn has now been heard in lambs, calves, and foals. More recently, Burnard (personal communication) has found cardiac murmurs in the majority of newborn babies, though the significance of these murmurs has yet to be established.

There is now evidence of various kinds that the ductus arteriosus remains patent for some time after birth in the following mammalian orders: primates (man), carnivores (dog), artiodactyls (sheep and cow), and perissodactyls (horse). It is clear that the blood flows from aorta to pulmonary trunk, and that conditions may be such as to cause a continuous murmur from the ductus. The benefit of an augmented pulmonary blood flow can be considerable if the lungs are not uniformly efficient as in the newborn (Born *et al.*, 1955*b*). On the other hand failure of the ductus to close may impose a severe strain on the left heart, and inadequate ventilation of the lungs may cause a rise of pulmonary vascular resistance sufficient to reverse the direction of blood flow through the ductus. It is thus evident that the physiology of the neonatal circulation requires much further study in relation both to normal and pathological processes.

Summary

A cardiac murmur, characteristic of blood flow through a patent ductus arteriosus, was heard in calves and foals within a short time after birth, and persisted for many hours.

Occlusion of the ductus arteriosus abolished this murmur and caused a rise of systemic arterial pressure and a fall of pulmonary arterial pressure.

The conclusion that the ductus arteriosus was patent, and that blood flowed from the aorta to the pulmonary artery, was supported by measurement of the oxygen content of blood withdrawn from the great vessels.

We wish to thank the Nuffield Foundation for their continued support, and Professor G. H. Acheson for helping with some of the experiments. We are most grateful to Mr. J. Elliott, Dr. J. A. Laing, Professor A. Messerry, and Mr. H. B. Parry for providing calves and foals.

References

Adams, F. H., and Lind, J. (1957). *Pediatrics*, **19**, 431.
Born, G. V. R., Dawes, G. S., and Mott, J. C. (1955*a*). *J. Physiol.*, **130**, 191.
——, ——, ——, and Rennick, B. R. (1955*b*). *J. Physiol.*, **130**, 167.
——, ——, ——, and Widdicombe, J. G. (1955*c*). *Cold Spr. Harb. Symp. quant. Biol.*, **19**, 102.
Burnard, E. (personal communication).
Dawes, G. S., Mott, J. C., and Widdicombe, J. G. (1955*a*). *J. Physiol.*, **128**, 344.
——, ——, —— (1955*b*). *J. Physiol.*, **128**, 361.
Eldridge, F. L., Hultgren, H. N., and Wigmore, M. E. (1955). *J. clin. Invest.*, **34**, 987.
Handler, J. J. (1956). *J. Physiol.*, **133**, 202.
James, L. S., and Rowe, R. D. (1957). *J. Pediatrics*, **51**, 1.

THE NATURAL HISTORY OF VENTRICULAR SEPTAL DEFECT

BY

L. BROTMACHER AND MAURICE CAMPBELL

From the Cardiac Department, Guy's Hospital and the Institute of Cardiology

Received July 26, 1957

The classical picture of ventricular septal defect—striking physical signs of little importance but for the risk of bacterial endocarditis—was formerly accepted, though it rested mainly on the single case, without necropsy, described by Roger in 1879. Taussig (1947) suggested that the defects were of two types: low defects with the classical picture and high defects where there were likely to be large pulmonary arteries and some symptoms. Selzer (1949), studying 80 reported cases and 12 post-mortem records of the San Francisco Hospital, found no support for this anatomical distinction. He concluded that the effects depend on the size of the defect; and that with a small defect there is little hæmodynamic change, while with a large one there is overloading of the pulmonary artery and finally hypertrophy, strain, and failure of the right ventricle. He thought that cyanosis was absent from uncomplicated cases, and that its presence and the appearances during angiocardiography were sometimes more reliable guides than was the pathological specimen itself in distinguishing between acyanotic cases and those with Eisenmenger's complex.

In 1948, cardiac catheterization in one of our patients demonstrated that a septal defect was ventricular and not, as we thought, atrial. Since then we, like others working at the subject, have found many examples of ventricular septal defect with a large left-to-right shunt. Dexter *et al.* (1947), Handelsman *et al.* (1948), and Burchell *et al.* (1948) reported some cases, and Wood (1950) and Joly *et al.* (1951) found that large defects were common and small ones uncommon. Marquis (1950) stressed that they were often the cause of death in children. Wood *et al.* (1954) reviewed the history of the maladie de Roger and emphasized that the effects of the lesion depend on the size of the defect and the consequent size of the shunt.

The association with a high pulmonary arterial pressure has been widely recognized (Wood, 1950; Blount *et al.*, 1955; and Kjellberg *et al.*, 1955), but the natural history of the changes in the lesser circulation has received scant attention, one reason being the impracticability of making serial observations on individual patients. The present study is based largely on 75 patients who had catheterization, but another 100 in whom the diagnosis rests at present only on clinical grounds have been used in the section on age and sex incidence. Emphasis is laid on the course of the disease and on the changes in the size of the shunts and in the pulmonary pressure and resistance with age. Patients with central cyanosis are included and the possibility of the aorta being normally placed in some and over-riding in others has been disregarded.

Principles and Classification. Unless the aorta arises entirely from the right ventricle, the right-to-left shunt depends on functional rather than anatomical causes—on the relative pressures in the two ventricles rather than on whether the aorta is over-riding or normally placed. Even when it is anatomically over-riding it can receive little if any blood from the right ventricle as long as the pressure in the right ventricle is lower than in the left, and under such conditions there is a large left-to-right shunt through the defect. We shall try to show that as the right ventricular pressure (which is often high in small children) rises further and as the pulmonary arteriolar resistance rises, this shunt becomes smaller and may ultimately be mixed with or replaced by a right-to-left shunt with an aorta that is now functionally over-riding.

Cases of the maladie de Roger (Group 1) and of Eisenmenger's complex (Group 5) are, therefore, the two ends of a continuous series of cases of ventricular septal defect: we think these two eponymous terms, and still more the term Eisenmenger's syndrome used by Wood (1956), have outlived their usefulness and should no longer be used in clinical medicine. Ventricular septal defects may be classified as follows.

(1) Small defects with a small left-to-right shunt only (up to 3 or perhaps 3·5 litres a minute). 9 cases.
(2) Larger defects with a left-to-right shunt of 4–15 litres a minute, still with a normal pulmonary arterial pressure. 6 cases.
(3) Larger defects with pulmonary hypertension that is hyperkinetic, with a left-to-right shunt only. 21 cases.
(4) Larger defects, still with a left-to-right shunt only and with pulmonary hypertension that is due to increased pulmonary arteriolar resistance (above 3 units). 12 cases.
(5) Larger defects with a right-to-left shunt also. Here the aorta is functionally over-riding; it may always have been anatomically over-riding or may have become so. 27 cases.

The figures show how many of our 75 cases belonged to each group: if we included those where the diagnosis rests on clinical grounds alone, Groups 1–4 would be enlarged much more than Group 5, but any further subdivision would be very uncertain (see Table III). Our classification represents to some extent the stage that has been reached rather than a permanent division. Cases in Group 1 and possibly in Group 2 remain there and some in Groups 4 and 5 may always have been there but with the passing of time cases in Groups 3 and 4 tend to pass to Group 5.

Most authors who have written on the subject recently have adopted a classification somewhat similar to this. Selzer (1954) made his main division between those where the pressure in the right ventricle was substantially equal to that in the left and those where it was less: he subdivided the latter into those with a small shunt and no rise of pressure and those with a larger shunt and some rise, and the former into those with a shunt that was still left-to-right only and those with a right-to-left shunt also. Wood (1954 and 1956) added the important distinction of a rise of pressure that was hyperkinetic only, making this his third group, and his fourth those with a " severe V.S.D." with raised pulmonary vascular resistance: he did not include cases with a right-to-left shunt, which would have made a fifth group. With this addition, his classification is substantially the same as ours, except that our second group, like the first, contains only those with a normal pulmonary pressure: if this is raised we think they are better in the third group because the rise is generally considerable. The dividing line between our groups 4 and 5 is such a narrow one, with patients moving across when they change from resting to exercising, that the cyanotic cases must be included in any classification of ventricular septal defect. The five groups of Mannheimer *et al.* (1957) correspond roughly with our five but we think ours are made more precise by using the pulmonary resistance.

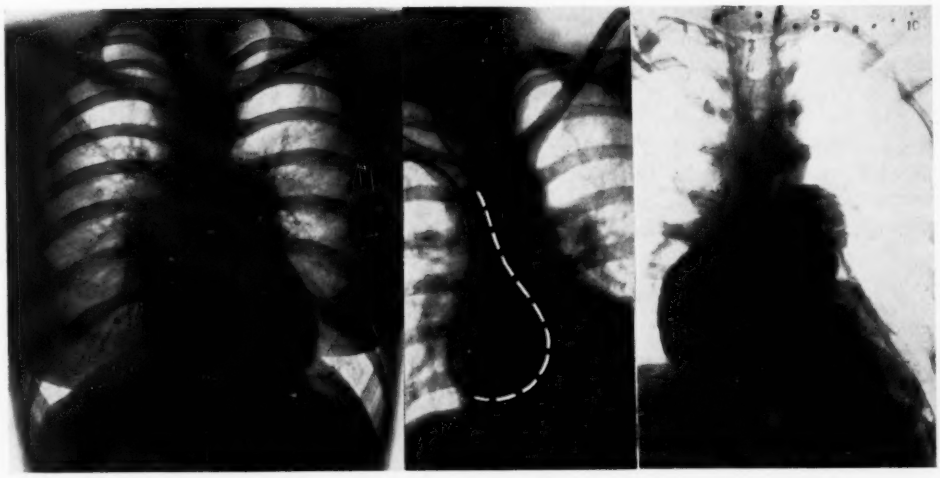
The following patient (Case 44, Table VI) is a good example of the natural history. As a girl, she led a normal life and no comment was made on her heart, even when she joined the W.A.A.F. at the age of 17 years. Her first symptoms started then during her physical training: she became breathless and cyanotic on exercise and fainted several times. She was discharged on these grounds and worked as a typist, but gradually became rather worse.

When 21, she came in for investigation: her cyanosis could hardly be seen when she was resting in bed, but increased greatly with exercise. The finger nails showed striking curvature but only slight clubbing otherwise, the characteristic beak fingers of slight or intermittent cyanosis. Her heart was not generally enlarged (c.t.r. 48%) though the right ventricle was; and the pulmonary arteries showed increased pulsation (Fig. 1).

Her arterial oxygen saturation was 92 per cent at rest and 85 during catheterization, but fell to 50 per cent with exercise, confirming that the right-to-left shunt, which was trivial at rest, became large with exercise. There was also a large left-to-right shunt (O_2 saturation: R.A. 48; low R.V., 56; mid R.V., 62; high R.V. 68; and P.A. 67%). The catheter passed easily from the right ventricle into the aorta (Fig. 1B): the pressures in both sides of the heart were substantially the same (aorta 103/71; P.A. 101/56, and R.V. 103/8 mm. Hg. Five years later, she could still earn her living and walk a mile, but was rather more breathless and cyanotic.

Cyanotic Patients

Of our 75 patients, 23 had central cyanosis even at rest and an arterial O_2 saturation under 90 per cent. It was between 90 and 96 per cent at rest in another 4 who were borderline and have been included with the cyanotic group, for two were generally cyanotic at rest with hæmoglobin percentages of 107 and 109 and two became cyanotic on exertion. Even among the acyanotic patients there was sometimes a dusky hue that made it hard to exclude a minimal degree of central cyanosis, and the arterial O_2 saturation was more often between 90 and 94 per cent than in most clinically acyanotic conditions. Many of these probably had small right-to-left shunts and these are shown in Table VI.



A B C

Fig. 1.—(A) Teleradiogram from a woman, aged 21 at the time she was developing a reversed shunt from pulmonary hypertension, showing a normal-sized heart and pleonæmic lung fields. (B) The catheter has passed from the right ventricle to the aorta and from there to the innominate and right carotid arteries. (C) Simultaneous filling of the aorta and its branches and of a rather large pulmonary artery before there has been significant filling of the left ventricle at angiocardiography. All Case 44.

The cyanotic patients included a much larger proportion of adults for more than half were over 20 years of age (see later). It was difficult to be sure when their cyanosis started and this in general will have to be established by direct observation. Five of the 12 children seemed to have been cyanosed from infancy and the other seven from somewhere between the ages of 4 and 10. In one boy, aged 14, and in one girl, aged 13, who were under regular observation, it was first noted when they were 8 years old.

Nine of the 15 adults gave a story of some tendency to cyanosis from infancy or childhood, but some of these may have had peripheral cyanosis that became central later. Several of these had no doubt that they had become much bluer a few years before they were seen (probably the start of central cyanosis), often at the time when they became more disabled. But an equal number reported cyanosis from childhood without any great change later. The remaining six gave a more precise history of the onset of cyanosis: their average age was 33 (range 21–45) and it had started at an average age of 29 (range 17–40). In two the observations seemed completely reliable: in the girl who has been quoted it started at 17, and in a woman, aged 31, her central cyanosis started at 29 and before this had been peripheral only.

On the whole, the cyanosis was not severe as judged by the standards of Fallot's tetralogy: in five the arterial O_2 saturation was between 75 and 79 per cent, in nine between 80 and 84 per cent,

LIBRARY
Ramsey County Medical Society
ST. PAUL, MINN.

in nine between 85 and 90 per cent, and in four (all borderline cases) above this. Corresponding to this, the mean hæmoglobin percentage was 115 with a usual range from 100 to 129 per cent. This is rather less than in simple pulmonary stenosis with a right-to-left shunt through an unsealed foramen ovale, where the mean was 120 with a usual range from 100 to 139; and much less than in Fallot's tetralogy, where the mean was 134 with a usual range from 120 to 149 per cent (Campbell, 1954).

Transposition. The transition from the acyanotic to the cyanotic form of ventricular septal defect is generally a gradual one. In the same way it may be difficult clinically to distinguish the latter from cases of transposition of the aorta and pulmonary trunk, especially when this is partial. When cyanosis has been present from birth it may be difficult to decide to which group a patient belongs, even after catheterization. Most such patients have probably been excluded from this series by confining it to those where the pulmonary artery was entered from the right ventricle. Difficulty may, however, arise when the aorta alone is completely transposed to the right ventricle.

Age and Sex Incidence

Age Incidence. More than three-quarters of our 175 patients were under twenty and more than half under ten years of age. The age incidence in the acyanotic and cyanotic patients was, however, very different: only 10 per cent of the acyanotic were over 20 but nearly half the cyanotic were over this age (Tables I, II, and III).

TABLE I
Age Incidence of Acyanotic Cases of Ventricular Septal Defect

Age (in years)	Number of cases				Percentages	
	Present series *	Wood (1956)	Selzer (1949)	Total	Acyanotic	All cases
0–10	25	37	52 †	114	54	46
11–20	19	22	16	57	27	23
21–30	2	7	7	16	7·5	13
31–40	2	4	9	15	7	12
41 and over	0	2	8	10	4·5	6
Total ..	48	72	92	212	212	300

* Our series was classified as 0–9, 10–19, etc., but the others as 0–10, 11–20, etc., but the error introduced by combining them in Tables I and II is not thought to affect our conclusions.

† Twenty-six were under one year of age and this high incidence in infants was also found in the series of Becu *et al.* (1956).

TABLE II
Age Incidence of Cyanotic Cases of Ventricular Septal Defect

Age (in years)	Present series *	Wood (1957)	Selzer and Laquer (1951)	Total	Male	Female	Percentage
0–10	7	12	6	25	16	9	28
11–20	5	5	3	13	8	5	15
21–30	5	13	4	22	9	13	25
31–40	7	6	7	20	8	12	23
41 and over	3	2	3	8	2	6	9
Total ..	27	38	23	88	43	45	—

* See note to Table I.

TABLE III
AGE INCIDENCE OF 100 CASES OF V.S.D. WITH CLINICAL DIAGNOSIS ONLY

Age (in years)	Acyanotic cases: estimated size of shunts						Cyanotic cases		Total	
	Small		Moderate		Large					
	M	F	M	F	M	F	M	F	M	F
0– 9	7	5	25	13	5	6	2	1	39	25
10–14	1	3	2	1	2	1	3	2	8	7
15–19	2	2	2	4	—	—	—	1	4	7
20 and over	2	2	1	3	—	—	1	1	4	6
Total ..	12	12	30	21	7	7	6	5	55	45

M=Male patients. F=Female patients.

As the number of our proved cases was relatively small we have combined them with the similar series of Wood (1956 and 1957) and with the necropsy series of Selzer (1949) and of Selzer and Laquer (1951) making 212 acyanotic and 88 cyanotic cases. Nearly half of the 300 were under 10 years of age, nearly three-quarters under 20, and only 6 per cent over 40 (see Table I). Clearly from these figures the outlook for longevity is poor, only 31 per cent having reached 20 and 18 per cent 30 years of age—a prognosis that is much worse than that of atrial septal defect or persistent ductus but better than that of Fallot's tetralogy. There are patients with defects so small that they are hardly significant, but they are not many. It is difficult to understand how the myth that all ventricular septal defects were minor lesions of little or no importance can ever have been accepted.

In these three series, which have the same general trends (see Tables I and II), the age incidence of the acyanotic and cyanotic cases separately is very different. Among the acyanotic there was a rapidly diminishing incidence in the first four decades, the figures being 54, 27, 8, and 8 per cent: among the cyanotic this was much more even, the figures being 28, 15, 25, and 23 per cent. This type of age incidence can be found only with a condition that is not lethal—and no one has suggested this of cyanotic ventricular septal defect—or with one that is replenished by fresh cases as some of the earlier ones die. It must, therefore, represent a steady change of cases from acyanotic to cyanotic and, as our experience suggests, this often happens in the first three decades. Taussig (1947) says that cyanosis appears most often " about the age of 15 " and that after this the patients may live for ten years but not often for much more. If we may change her 15 years to between 5 and 25 or perhaps 30, we agree with this terse summary.

Sex Incidence. In our series girls and women were rather more frequent than boys and men, the proportions being 3 : 2, but if the 100 cases where the diagnosis was made on clinical grounds alone (see Table III) are included, the sex incidence was equal, as it was in the series of Selzer (1949) and of Wood (1956). This equal incidence in the groups as a whole conceals some points of interest, to which we have found no references.

(1) More of our patients with a normal pulmonary arterial pressure were girls or women—among the proved cases all except one man aged 23.

(2) There were far more women than men over twenty. Among the proved cases a third of the women (17 of 46) and less than a tenth of the men (2 of 29) were over this age; or, if the clinical cases are included, one-quarter of the women and less than a tenth of the men.

(3) The female patients who had become cyanotic were older than the male patients: 14 out of 16 of the former were over fifteen and 9 out of 11 of the latter were under this age. This was equally true if the clinical cases were included.

Unless our series is atypical, the rise of pressure must occur sooner or be less well supported by boys than by girls, fewer of the boys surviving to adult life. The question is of practical importance for it would clearly follow that if life is to be saved, operation is indicated earlier and more urgently in boys than in girls (see later). More evidence is needed, for though we have seen few boys with a normal pressure, the rise of pressure with age in Groups 3–5 seems to be similar in the two sexes (see Fig. 7).

Elsewhere we have not found many data to support these differences and in the series of Wood (1957) there were rather more men than women over 20. However, in the cyanotic cases reported by Selzer and Laquer (1951), the male patients were equally divided into those under fifteen and those over twenty: while there were only 2 girls under fifteen but 9 women over twenty: the difference in the average ages at death was 9 years (22 against 31). If the three series are combined there are 29 cyanotic boys (up to twenty) and 18 cyanotic girls, but over twenty there are 20 cyanotic men and 32 cyanotic women. The ratio of male to female patients was 1·7 to 1·0 under twenty and 0·6 to 1·0 over twenty. It seems unlikely that this difference could arise by chance when considering 99 cyanotic patients and it was almost the same if our 11 clinical cases were omitted.

Clinical Picture

Diagnosis. The systolic murmur and thrill are harsher and more striking than with atrial septal defects (A.S.D.) and are generally maximal lower, in the fourth left space: the pulmonary second sound is much less widely split. If, however, these signs are present without pleonæmic lungs on radioscopy, their significance must remain uncertain. We agree with Wood *et al.* (1954) that other lesions are proved to be present more often than a ventricular septal defect in cases where this was suspected on clinical grounds alone. We have many more patients of this type among our cases diagnosed clinically, sometimes wrongly, as for example one who has just been shown to have a trivial infundibular stenosis, than among those who have been proved, but few patients without symptoms have been catheterized.

The electrocardiogram does not help much in diagnosis. There may be an rSR′ complex but much less often than with A.S.D. Either the left or the right ventricle or both may show hypertrophy, and as Mannheimer *et al.* (1957) have pointed out, combined ventricular *hypertrophy* is the most common finding in cases corresponding to our groups 3, 4, and 5. Extreme right ventricular *preponderance* and strain are less common than they are in cases of A.S.D. with the same degree of pulmonary hypertension.

Where the site of the septal defect has been in doubt radioscopic evidence of left ventricular enlargement has, however, generally proved a correct indication that the defect is ventricular, but if the right ventricle is very large the left ventricle may appear wrongly to be a little large because it has been pushed over.

The Size of the Heart. This varies greatly—from normal to very large. We have divided the patients into four groups in Table IV—those who have a normal pulmonary arterial pressure, those who have pulmonary hypertension but are acyanotic, those who are cyanotic, and those who have aortic regurgitation.

The cases with a normal pulmonary pressure were almost equally divided into those with normal, slightly enlarged, large, and very large hearts (see Table IV). The normal-sized hearts were, as might be expected, in those with the smaller shunts (Fig. 3A). Among the acyanotic cases with a raised pulmonary pressure and a large or moderate shunt, the hearts were with one exception enlarged (Fig. 2) and more than half were very large (c.t.r. 60% or more)—as large as in cases of A.S.D. with shunts of the same size. By contrast, among the cyanotic cases, both children and adults, a large heart was much less common. It was of normal size in more than a quarter—a larger proportion than in any other group—and very large in less than a quarter (Fig. 3, B and C).

This high incidence of normal-sized hearts in cyanotic patients is difficult to understand. If at an earlier stage they have been acyanotic with a large left-to-right shunt they might be expected

TABLE IV

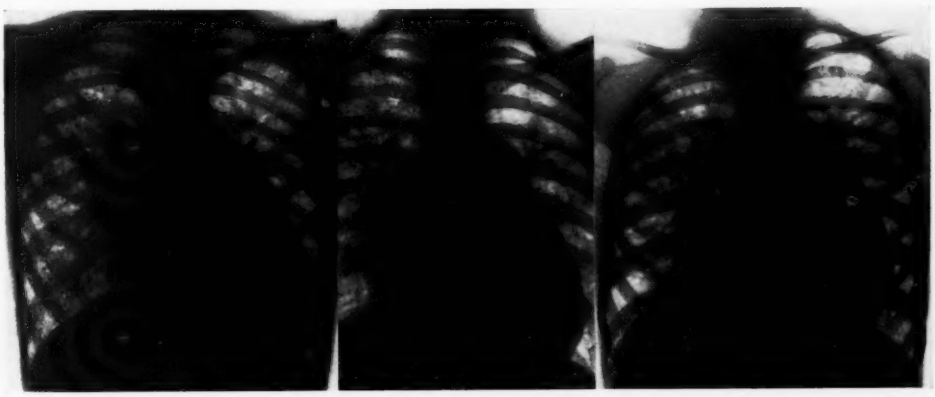
THE SIZE OF THE HEART IN VENTRICULAR SEPTAL DEFECT

Groups	Heart size			
	Normal (c.t.r. 50% or less)	Slightly enlarged (51–54%)	Large (c.t.r. 55–59%)	Very large (c.t.r. 60% or more)
1 and 2. With normal P.A. pressure (15) ..	4	4	5	2
3 and 4. With raised P.A. pressure but no cyanosis (30)	1	5	8	16
5. With raised P.A. pressure and central cyanosis (27)	8	1	12	6
With added aortic regurgitation (3)	0	0	0	3
Total	13	10	25	27

to have a large heart, but this does not seem to happen, though it does with similar cases with A.S.D.

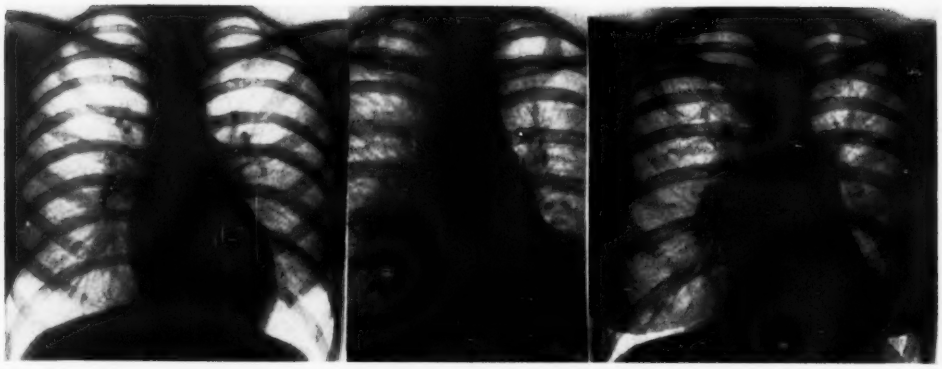
Only two explanations are possible and we think each applies on occasion: that a large heart has become smaller, when the shunt and pulmonary flow have become smaller: or that the cyanotic patients have never had left-to-right shunts large enough to produce a large heart. In the latter case, even if they were not cyanotic from infancy, the pulmonary pressure may always have been high enough to prevent a large shunt, and then the right ventricle may be hypertrophied without much increase in the size of the heart. Similarly, the heart is often of normal size in cases of persistent ductus with a reversed shunt, in most of whom there is more evidence of pulmonary hypertension and consequent absence of a large left-to-right shunt even in infancy (Campbell, 1955).

On the other hand the fact that all the borderline cases where cyanosis was developing had large hearts (c.t.r. 57–67%) and that two were observed becoming smaller (c.t.r. 60 to 55% and 59 to 55%; Fig. 4) supports the former possibility. Until this has been observed more often and in adults, it is not easy to accept a large heart becoming of normal size when the patient is becoming worse, but we think this happens in some cases.



A B C

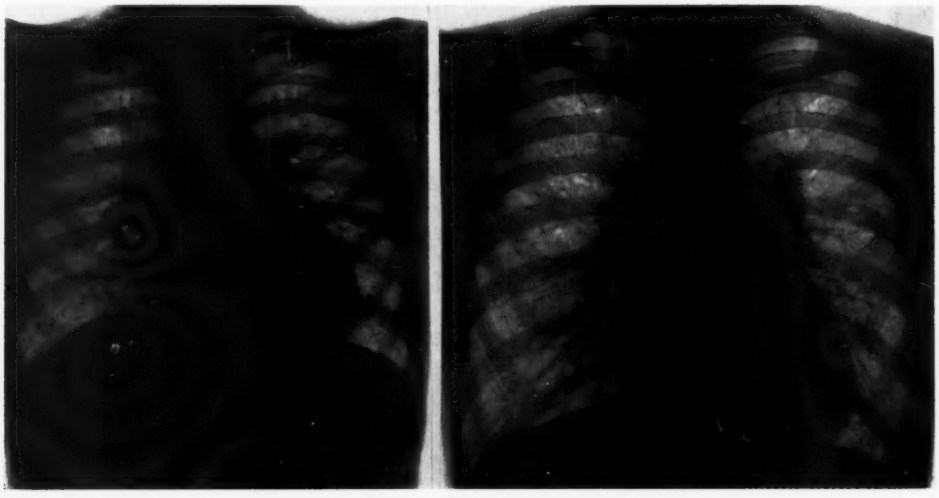
FIG. 2.—Large hearts from three acyanotic children with large left-to-right shunts. (A) From a boy of 11 with a c.t.r. of 65 per cent and a pulmonary arterial pressure (PAP) of 72/43 (Case 31). (B) From a boy of 11 with a c.t.r. of 56 per cent with a PAP of 90/60 (Case 39). From a girl aged 10 with a c.t.r. of 66 per cent and a mean PAP of 78 mm., who died two years later (Case 0165). The rise in PAP was hyperkinetic in (A) and (B).



A B C

FIG. 3.—Three hearts that are more varied in size. (A) From a girl of 14 with a small defect, a small shunt, and a normal PAP. The heart was of normal size, as always in this type. (B) and (C) show two hearts, one enlarged and one of normal size, in cyanotic adults with pulmonary hypertension. (B) From a woman aged 36 with a c.t.r. of 58 per cent and a PAP of 155/95, the highest recorded in our series, where the pressures and shunts seemed balanced (Case 54). (C) From a woman aged 34 with a heart of normal size (c.t.r. 50%): the PAP was 112/62 and the shunt was right-to-left only. She had certainly been cyanotic since she was 30 and probably since she was 21 (Case 52).

In general, the heart is large in patients with large left-to-right shunts and becomes smaller when these are abolished by surgery. In Fallot's tetralogy, conversely, when the pulmonary flow is increased by operation the heart becomes larger, and we have found that if the anastomosis closes the heart may become smaller again. A rise in stroke volume causes cardiac hypertrophy and dilatation, whereas increased work against a raised pressure causes hypertrophy without any general enlargement.



A B

FIG. 4.—A heart that became smaller after four years, both as regards the cardiothoracic ratio and the relative area of heart and thorax. (A) At the age of five. (B) At the age of nine when the PAP was 106/64 and the arterial O_2 85 to 88 per cent (Case 25).

In our cyanotic cases, a right-to-left shunt was generally associated with a low pulmonary flow, and never with a large one (see Table VI), and therefore with a normal right ventricular stroke volume. In consequence, reduction in the left-to-right shunt, even if accompanied by a rise in pulmonary pressure, might lead to the heart becoming smaller.

Pulmonary Regurgitation. This diagnosis was made in 19 of our 75 patients. Three others had aortic regurgitation (see later). In some there was a question of whether the regurgitation was aortic or pulmonary, because of the site of the murmur, the wide pulse pressure, or the appearance on radioscopy; but it was accepted as pulmonary because not more than one of these features was present in any case. Pulmonary regurgitation was less common in the younger patients—in one-sixth of those in the first decade but in nearly one-third in later decades. In one boy who already had a large heart and pleonæmic lungs when he was two and was under regular observation, it was first observed when he was ten at a time when the pulmonary pressure was 72/43 mm. (Case 31).

On the whole pulmonary regurgitation does not seem to add greatly to the patient's handicap and some in whom it has been present for seven years are still doing well. It was observed in only one patient where the pulmonary arterial pressure was normal but in over one-third (18 of 49) of those where it was raised. It is nearly three times as common as in A.S.D. where it was found in one in eight (Campbell *et al.*, 1957). If, however, we allow for the smaller proportion of these patients who develop a raised pressure, its incidence in those with pulmonary hypertension is almost the same in those with atrial (7 of 18) and in those with ventricular septal defects (18 of 49)—rather more than one-third in each group.

Aortic Regurgitation. The association of this with ventricular septal defect has been recognized for some time (Laubry and Pezzi, 1921; Laubry *et al.*, 1933; Routier *et al.*, 1949). Generally the defect causes deformity of a cusp of the aortic valve and the regurgitation may be extreme.

We had no doubt of this diagnosis in three of our patients. One has an enormous heart (c.t.r. 69%) but it has remained the same for nine years and he is able to lead a quiet life and go to school during the summer. The other two, however, have died (Cases 8 and 60, see p. 106). Clearly, it is a serious complication because both lesions are throwing a heavy strain on the left ventricle.

The Side of the Aortic Arch. The aortic arch was left-sided in all but two of our patients. These two, women aged 23 and 26, had been cyanotic from childhood (Cases 46 and 47). We do not think that they had any degree of transposition, but have seen other cases with a right-sided arch where the diagnosis of cyanotic V.S.D. was considered but replaced by that of partial transposition of the aorta and pulmonary trunk. Among the 100 patients diagnosed on clinical evidence only, two had a right-sided aortic arch: neither had shown any signs of becoming cyanotic when last seen, one aged 10 and the other aged 25 years. At least three patients had a left-sided superior vena cava (Cases 1, 7, and 27).

Changes of Rhythm were uncommon. Auricular fibrillation was found in one man, aged 30 years. Congenital heart block was found only in one cyanotic woman, aged 30; it has been rare in other series, confirming the view of Campbell and Thorne (1956) that the reputed association of heart block and ventricular septal defect is much less common than has been thought. There was, however, one boy aged 12, with pulmonary stenosis in addition (not, therefore, included in this series) who had at times complete and at times 2 : 1 heart block.

Course and Prognosis

Patients with small shunts and normal pulmonary pressures were generally free from symptoms. Most of those with larger shunts and a raised pressure were limited in what they could do but not as a rule seriously. Several of the older patients had carried on successfully with light work until they developed central cyanosis, but not for long after this. Even then, the downhill course was slower than we expected and often lasted for several years: some had recurrent hæmoptyses during this stage. It seems that these patients tolerate a high pulmonary pressure better than those where it is secondary to atrial septal defect. We think, however, that they are more disabled and have a worse outlook than most patients of comparable age with A.S.D.

Patients who have Died. Nine of these patients are known to have died before they were twenty-five. It is true that three of them died after operation, that two had congestive failure from aortic regurgitation, and that two had additional lesions (pericarditis and ruberculosis); but they were ill patients before these terminal events and some already had congestive heart failure and others very large hearts so that we do not think they would have lived for long.

These patients represent the group who die young because they cannot support a shunt that is unusually large or because they fail to make the necessary adaptations. At least two of the older patients also have died.

One child died at the age of 3 (Case 16) and three others had severe symptoms that were getting worse though they actually died after operation (Cases 13, 18, and 26). All these four had enormous hearts which in three had been observed to increase in size (c.t.r. 71%, 61 to 68%, 62 to 75%, and 65 to 73%); all had a pulmonary pressure of about 75/50, not greatly below the systemic pressure.

Two boys, both aged 9, were fairly well until the onset of congestive failure a few months before their deaths (reported by Baylis *et al.*, 1955): one with added aortic regurgitation had an enormous heart (c.t.r. 59 to 76%) and remained acyanotic (Case 60), and the second became slightly cyanotic only during his last weeks (Case 27).

A girl, aged 15, also had a very large heart with free aortic regurgitation; she had no congestive failure while under observation but was becoming worse and died three years later: this was said to be from nephritis but we have not been able to get any details (Case 8). A girl, aged 10, had congestive heart failure when last seen two years before her death: at necropsy there was pericarditis, possibly rheumatic, but again we have no details except that it confirmed the diagnosis of V.S.D. The ninth, a boy aged 17, was cyanotic and moderately disabled: six years later he died with broncho-pneumonic tuberculosis and there was a large V.S.D. at the usual site (Case 42).

The tenth, aged 34, had been more disabled for two years and cyanotic since childhood; and the pulmonary pressure was 155/95, about the same level as the systemic: she died four years later with pulmonary congestion and hæmoptyses (Case 54). The eleventh, aged 47, did domestic work till four years before: she was only a little cyanotic but died two years later (Case 57).

Hæmodynamic Aspects

In this section we are including 57 (Tables V and VI) of the 75 patients discussed so far: 38 were catheterized at Guy's Hospital and 19 at other centres, mainly the National Heart Hospital. We are omitting (a) six who have been catheterized since the tables and diagrams for this section were completed, (b) four where the data of catheterization were incomplete, and (c) eight where a

TABLE V

Hæmodynamic Data in Patients with a Normal Pulmonary Arterial Pressure

Case No.	Sex and age	Surface area (sq. m.)	Systemic flow (l./min.)	Pulm. flow (l./min.)	Left-to-right shunt (l./min.)	Pressure (mm. Hg)		Resistance (units)	Arterial sat. (%)
						Pulm. artery; mean (in brackets)	Mean pulm. cap.		
1	F 5	0·78	2·2	4·2	2·0	29/9 (20)	7	3·1	—
2	F 5	0·74	5·3	10·2	4·9	21/12 (17)	12	0·4	100
3	F 6	0·78	2·5	6·0	3·5	18/9 (12)	—	0·9	100
4	F 7	0·82	3·8	7·2	3·4	27/8 (10)	3	1·0	92
5	F 7	0·89	3·6	5·3	1·7	23/15 (17)	8	1·7	96
6	F 7	—	— *	— *	—	25/18 (20)	—	—	—
7	F 10	0·82	4·7	13·3	8·6	20/16 (19)	13	0·5	94
8	F 15	1·08	4·5	12·1	7·6	33/16 (24)	—	1·6	99
9	F 16	1·55	5·8	7·8	2·0	18/5 (10)	—	0·6	99
10	F 19	1·46	5·2	6·7	1·5	20/8 (14)	9	0·7	92
11	M 23	1·90	5·3	21·4	16·1	19/11 (13)	8	0·2	95
12	F 39	1·38	4·0	6·2	2·2	26/11 (16)	—	1·8	98

* Not calculable owing to error in estimating arterial oxygen content.

TABLE VI
HÆMODYNAMIC DATA IN PATIENTS WITH A RAISED PULMONARY ARTERIAL PRESSURE

Case No.	Sex and age	Surface area (sq. m.)	Systemic flow (l./min.)	Pulm. flow (l./min.)	Shunt (litres/min.)		Pressure (mm. Hg)		Mean pulm. cap.	Resistance (units)	Arterial saturation (%)
					L.→R.	R.→L.*	Systemic	Pulm. artery (mean in brackets)			
13	F 1	—	— †	— †	Present	Probably absent	—	75/50 (60)	—	—	—
14	M 1	0·41	4·4	8·0	4·0	0·4	80–90/—	74/44 (69)	—	7·3	92
15	M 3	0·60	2·2	8·0	5·8	0	110/70 ‡	55/27 (32)	—	2·5	98
	M 10	0·92	4·3	11·1	6·8	0	80/54	55/24 (36)	—	2·6	96
16	M 3	0·58	1·6	3·3	1·7	0	72/4 (L.V.)	73/47 (58)	—	14·2	98
17	M 4	0·68	3·4	4·4	1·0	0	110/80 ‡	62/55 (57)	—	10·4	100
18	M 5	0·72	2·7	8·4	5·7	0	90/70 ‡	67/45 (55)	8	5·6	—
19	M 5	0·68	2·1	7·1	5·6	0·6	100/70 ‡	88/50 (70)	—	8·3	90
	M 12	1·06	3·1	2·8	1·3	1·6	110/80 ‡	120/65 (90)	—	23·3	67
20	M 6	0·82	3·7	6·8	3·9	0·8	64/49	70/39 (53)	10	6·3	90
21	F 6	0·74	4·4	5·5	2·0	0·9	102/50 ‡	60/38 (50)	—	7·1	91
22	M 8	0·92	6·0	2·7	0	3·3	78/59	68/54 (61)	—	18·6	80
23	F 8	0·75	3·8	18·8	15·0	0	106/66 ‡	87/40 (59)	—	2·6	94
24	M 8	0·85	5·5	8·1	3·2	0·6	100/70	94/54 (70)	—	7·3	93
25	F 9	0·94	7·8	7·2	3·1	3·7	106/68	106/64 (78)	16	8·7	85
26	M 9	0·81	2·9	4·8	1·9	0	120/70	94/54 (67)	22	9·4	96
27	M 9	0·88	4·1	4·1	0·5	0·5	95/75	94/64 (82)	—	17·2	93
28	M 10	0·87	3·2	9·8	6·6	0	90/60	58/29 (45)	9	3·7	—
29	F 11	0·96	4·4	24·0	19·6	0	110/75	93/40 (60)	—	1·9	99
	F 18	1·42	4·0	20·0	16·0	0	85/55	85/30 (55)	—	2·2	94
30	M 11	1·24	4·0	2·8	0·3	1·5	110/85	107/76 (86)	7	28·2	84
31	M 11	0·88	3·9	V. large	V. large	0	95/—	72/43 (56)	—	—	97
32	M 12	—	7·1	5·0	3·2	1·1	105/—(L.V.)	130/70 (85)	—	14·6	81
33	M 12	1·26	4·0	6·7	2·7	0	—	97/61 (79)	10	10·3	—
34	F 12	1·32	3·9	7·9	4·0	0	100/78	102/71 (81)	—	8·8	97
35	M 13	1·15	4·6	19·7	15·1	0	95/65	83/35 (54)	—	2·2	97
36	F 13	0·97	5·1	5·5	1·4	1·0	95/53	95/60 (71)	—	10·7	90
37	F 14	1·37	5·0	2·6	0·3	2·7	100/75 ‡	120/68 (90)	—	30·3	83
38	M 14	1·20	3·3	4·6	2·1	0·8	112/80	100/44 (65)	10	12·0	88
39	F 15	1·28	4·8	27·0	22·2	0	90/60	95/35 (62)	—	2·4	94
40	F 16	1·54	2·8	18·7	15·9	0	95/50	82/58 (68)	—	3·0	—
41	M 16	1·34	6·3	11·1	5·6	0·8	105/65 ‡	63/27 (42)	16	2·3	93
42	M 17	1·15	5·2	5·0	2·1	2·3	100/60 ‡	95/60 (72)	—	12·2	82
43	F 18	1·58	4·7	13·9	9·2	0	120/60	103/61 (80)	—	4·9	99
44	F 21	1·34	— †	— †	Present	Present	103/71	101/56 (71)	—	—	85
45	F 22	1·37	3·7	8·1	4·8	0·4	125/57	105/57 (77)	—	8·2	93
46	F 23	1·42	3·1	2·8	1·2	1·5	130/80	95/55 (71)	—	21·4	77
47	F 26	1·48	7·7	4·8	1·5	4·4	116/81	116/81 (96)	—	17·7	77
48	M 30	1·72	4·3	4·7	2·1	1·7	145/77	125/75 (92)	—	17·0	78
49	F 31	1·59	5·6	3·9	0	1·7	92/43	100/55 (67)	20	12·0	86
50	F 31	1·48	3·5	29·4	25·9	0	118/76	95/31 (51)	2	1·7	95
51	F 33	1·45	3·9	3·0	0·8	0·9	120/90 ‡	116/55 (83)	—	24·0	81
52	F 34	1·52	4·4	3·0	0	1·4	110/60	112/62 (82)	—	23·3	87
53	F 36	1·54	6·2	5·3	2·0	1·1	110/80	88/32 (56)	7	9·2	79
54	F 36	1·44	2·2	—	—	—	140/90	155/95 (115)	—	—	84
55	F 39	1·44	3·6	3·2	0·9	1·3	121/66	121/56 (82)	—	21·9	78
56	F 44	1·51	5·3	4·0	1·8	3·1	115/80 ‡	122/55 (81)	—	17·4	82
57	F 47	1·22	3·7	6·4	3·5	0·8	120/65	128/56 (89)	—	12·2	87

* The overall shunt is obtained by subtracting the lesser of these from the greater.
† Oxygen consumption not measured.
‡ Not measured during cardiac catheterization.

small pressure gradient across the pulmonary valve prevented us using them for study of the relationship of the pulmonary artery pressure to age and other factors, even though we thought there was no organic stenosis. These last will be discussed with another 15 patients who had a left-to-right shunt through a ventricular septal defect and also a gradient that we thought significant of pulmonary stenosis (Brotmacher and Campbell, 1958).

Methods. General anæsthesia was employed in 13 subjects and barbiturate sedation in the remainder. Every attempt to secure basal conditions was made, and the oxygen consumption was within 25 per cent of normal for the age and sex in over 70 per cent of those where there were adequate data.

Pressures were measured from the mid-thoracic plane using Sanborn, Southern Instruments, or Hamilton manometers. Oxygen uptake was measured with a Benedict spirometer and the percentage saturation of the blood samples estimated by the Haldane method. In those patients with pulmonary hypertension in whom the catheter could not be wedged successfully, the pulmonary arteriolar resistances were calculated by using the mean of the measured pulmonary capillary pressures, which was 11 mm. Hg.

The oxygen content of the right ventricular blood was at least 1 ml. per 100 ml. higher than the right atrial in all the acyanotic patients, except one who developed ventricular tachycardia when the catheter was in the right ventricle. It was higher by this amount in 10 of the 18 cyanotic patients: in two of the other 8 the aorta was entered, in two simultaneous filling of the aorta and pulmonary artery was shown by angiocardiography and in four the diagnosis was based on clinical grounds and on a right ventricular pressure that approximated to the systemic.

The oxygen content of the pulmonary arterial blood exceeded the right ventricular sample by more than 0·5 ml. per 100 ml. in 12 patients, but this was attributed to a streaming effect rather than to a second shunt. In one of these a persistent ductus was excluded at autopsy, and in a second such case by aortography. This difference in oxygenation was observed by Bowers *et al.* (1955) also, in a patient where a communication between the aorta and pulmonary artery was excluded at operation.

Pulmonary Flows and Shunts

The pulmonary blood flows in the 51 patients where the data were available ranged from below normal (in patients with veno-arterial shunts) to values that were too large to be measured with any accuracy (Tables V and VI and Fig. 5). Among patients with a normal pulmonary arterial pressure

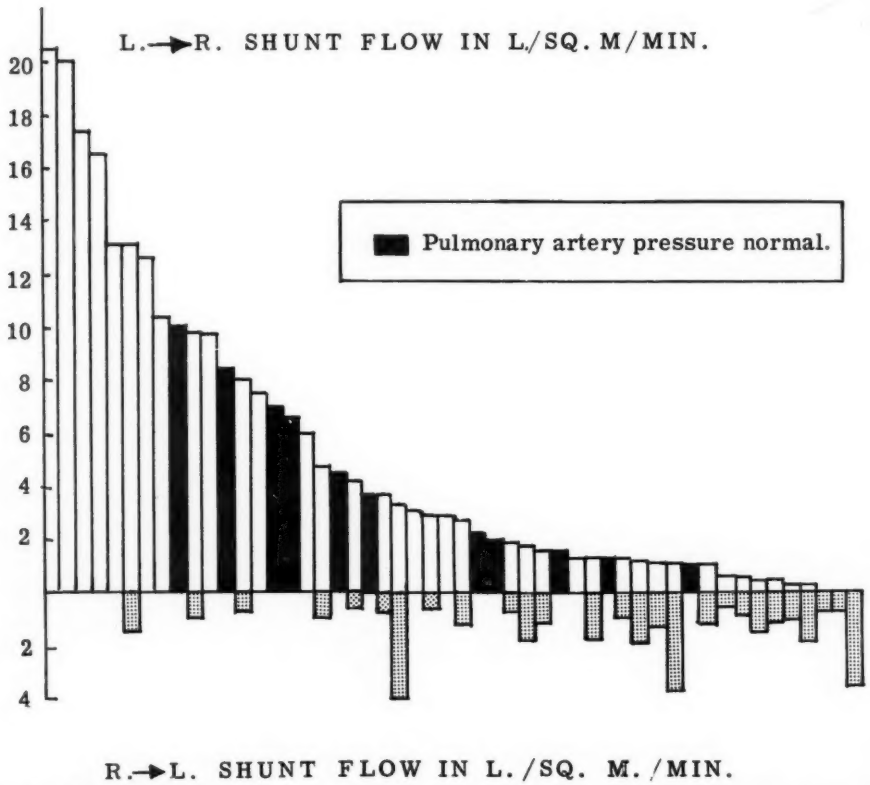


Fig. 5.—The size of the shunts in litres/sq. m./min. in ventricular septal defect. Above the line, the left-to-right shunts arranged in order of size; the dark shading shows the patients with normal pulmonary arterial pressures. Below the line, lightly shaded, the right-to-left shunts.

there were (1) 7 with shunts that averaged 2·4 litres a minute and (2) 4 with shunts that averaged 8·1 litres a minute, a shunt comparable with that in many cases of atrial septal defect.

(3) In 8 patients the rise of pulmonary pressure was hyperkinetic, the pulmonary resistance being under 3 units, and the average shunt was 15·6 litres a minute, which is comparable with the larger shunt of many cases of A.S.D.

(4) In 17 patients the pulmonary resistance was raised (generally between 6 and 12 units) and the left-to-right shunt was much smaller, but still averaged 3·5 litres a minute. There was sometimes also a right-to-left shunt that was still too small to make the patient frankly cyanotic.

(5) Finally, 15 cyanotic patients with a very high pulmonary resistance (nearly always over 12 units) had a right-to-left shunt large enough to lower the arterial O_2 saturation to 87 per cent or less. Even so, most of them had still a left-to-right shunt, but it averaged only 1·3 litres and could not be measured in three.

These groups overlap but give a general picture of the position. The proportion in each group is quite unlike what is found with atrial septal defect, where nearly all children and half the adults are in the first three groups and many fewer in the fourth and fifth (Campbell *et al.*, 1957).

The patients with the larger veno-arterial shunts were as a group older than the others, and with their inclusion the pulmonary flows and shunts were somewhat lower in adult life than in childhood and adolescence. Otherwise there was no relationship between age and pulmonary flow, whether the pulmonary pressure was normal or was raised. Even when patients with normal and with raised pulmonary resistance were considered separately, no age trends were discernible in the acyanotic group.

Arterial Anoxæmia

There were 19 patients with clinical cyanosis, associated with polycythæmia, clubbing of the fingers, or both. Significant arterial desaturation (to under 90 %) was seen only in conjunction with a high pulmonary arterial pressure (Fig. 6) and was therefore more common in older patients. It was seen in 2 of 21 patients in the first decade, in 5 of 20 in the second decade, and in 12 of 16 in the third decade and after—in one-fifth of those under 20 but in three-quarters of those over this.

Taussig (1947), in describing Eisenmenger's complex as a distinct entity, suggested a pulmonary factor as part cause for the arterial desaturation. However, a sample from the left atrium was between 94 and 100 per cent saturated in three patients (Cases 22, 32, and 55) in whom it was possible to manipulate the catheter into this chamber, the absence of shunting in either direction at atrial level suggesting that an unsealed foramen ovale had been intubated. Similar findings have been described by Soulié *et al.* (1953) and Kjellberg *et al.* (1955). In the 12 patients with pulmonary hypertension in whom pulmonary capillary pressure was measured, it was well below the levels at which extravasation of fluid is likely to interfere with oxygen uptake. We consider that the arterial oxygen desaturation can be accounted for entirely by the right-to-left shunt.

Pulmonary Arterial Pressure

The pulmonary pressure was normal in 12 (Table V) and raised in 45 of our patients (Table VI). The two groups are quite distinct (Fig. 7): in one there is no rise of pressure, in the other it is considerable, and there is no intermediate group with a slight or moderate rise of pressure. This clear-cut distinction appears to characterize the series of Wood (1950) and of Kjellberg *et al.* (1955) but not the series of Mannheimer *et al.* (1957) or Blount *et al.* (1955). Blount's patients are not strictly comparable, as they were observed at the high altitude of Denver; and perhaps for this reason did not include any with a normal pulmonary pressure.

Wood *et al.* (1954) have suggested that there is a critical size of defect, about 1·0 cm. in diameter, below which the pulmonary pressure is unlikely to rise much, and above which it is likely to approximate to that in the left ventricle. This concept is supported by the observations of Griffin and

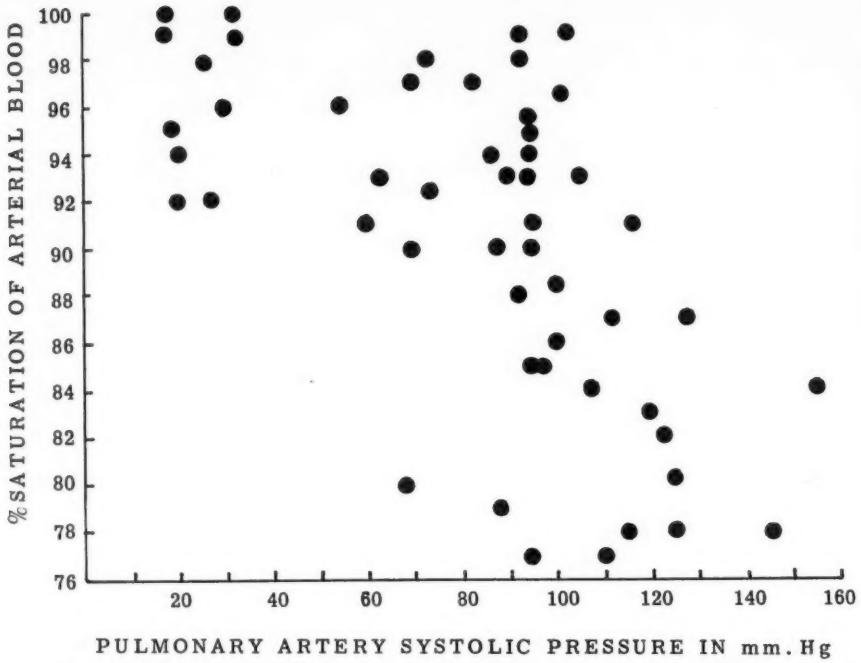


FIG. 6.—The relationship of the arterial oxygen saturation to the pulmonary arterial systolic pressure. Up to a systolic pressure of 85 mm. Hg most patients show normal arterial oxygen saturation and only one is under 90 per cent. Above 110 mm. Hg most show considerable desaturation and only one is *over* 90 per cent. At pressures between 85 and 110 mm. the findings are variable, this depending partly, no doubt, on the level of the systemic pressure in the patient concerned.

Essex (1951) who found that most dogs in which they produced a ventricular septal defect of 0·8 cm. survived while those in which it was 1·2 cm. invariably died. Probably patients with pulmonary hypertension are those whose defects are larger than this critical size and patients with normal pulmonary pressures those whose defects are smaller than this.

Only 7 of the 12 subjects with normal pulmonary pressures had shunts small enough to be included in our Group 1: in 4 (Group 2) the shunts were of moderate size, but the pressures remained normal because the pulmonary resistance was low. The systemic flows were about normal, from which it follows that, provided the shunt is not very large, a high resistance to pulmonary flow is not always essential for the maintenance of an adequate systemic flow. In 7 patients in these two groups the pulmonary capillary pressure was measured and found to be normal, so that pulmonary hypertension does not seem to play any vital part in preventing pulmonary œdema in ventricular septal defects, as has been postulated in mitral stenosis (Wood, 1954).

No tendency for the pressure to rise with age could be seen among the patients with a normal pressure: they were mostly under 20, but two were 23 and 39 years of age. Within the group with a raised pressure the systolic pressure tended to rise with age (Fig. 7A), the correlation being highly significant ($r=0{\cdot}69$, $t=6{\cdot}23$, $P<0{\cdot}001$). The mean increase was 1·3 mm. each year and it was rather more in the acyanotic than in the cyanotic cases. The rise in diastolic pressure was smaller and of doubtful significance ($r=0{\cdot}27$, $t=1{\cdot}84$, $0{\cdot}1>P>0{\cdot}05$): it averaged 0·5 mm. each year (Fig. 7B). We shall discuss the relationship of this rise to the normal rise of systemic pressure with age (see p. 113).

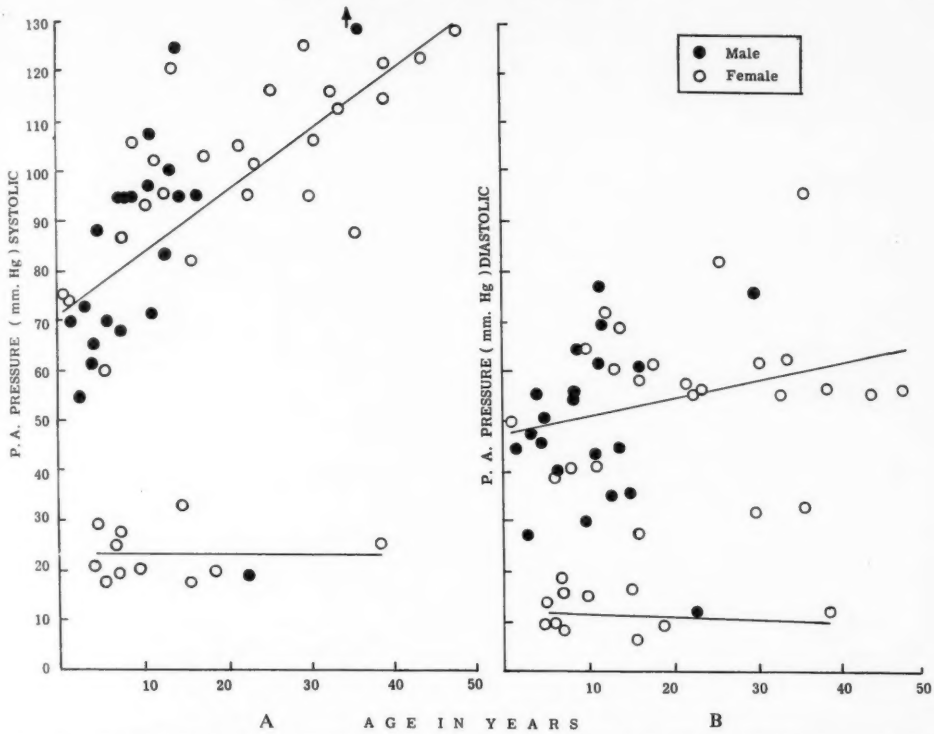


FIG. 7.—The relationship of pulmonary arterial pressure to age. (A) On the left, the systolic pressures are separated into two groups—those with a normal pressure where there is no tendency to rise, and those with a raised pressure where it rises progressively. (B) The diastolic pressure is shown on the right: it shows these two features, but much less than the systolic pressure does. The calculated regression lines are shown by continuous lines.

The fact that the systolic pressure rises more than the diastolic results in a rise in pulse pressure with age and a progressive increase in the ratio of the pulse pressure to the diastolic pressure. This was not due to the inclusion of patients with pulmonary regurgitation, for these did not have higher pulse pressures or lower diastolic pressures than those of corresponding age in whom the pulmonary valve was competent. This rise in pulse pressure suggests that decreasing distensibility of the pulmonary vascular bed plays some part. The smaller rise in diastolic pressure means that the pulmonary hypertension of an adult with a ventricular septal defect is more like the systemic pressure of 200/90 seen in an atherosclerotic patient than the pressure of 200/120 seen in one with essential hypertension.

No hæmodynamic basis for the difference in the age incidence of the two sexes (see p. 101) has been found; the pulmonary arterial pressures did not differ, when allowance was made for age (Fig. 7), and the mean pulmonary flow per square metre in the boys under 20 was actually a little less than that in the girls.

The rate of rise of pressure is greater in the acyanotic than in the cyanotic cases. Arterial anoxæmia and the changes in blood viscosity associated with polycythæmia are, therefore, not likely to be important. The mean systolic pressures of the cyanotic and the acyanotic groups were 112 mm. and 85 mm. respectively, but this difference can be largely accounted for by the mean age of the cyanotic patients being 24 and that of the acyanotic ones only 12 years. This, however,

does not explain the correlation between age and pulmonary pressure for it was found to retain its significance ($r=0{\cdot}65$, $t=4{\cdot}34$, $P<0{\cdot}001$) when the cyanotic patients were excluded from the analysis.

The higher pulmonary arterial pressure of the older patients suggests that it has increased with age, and so does the clinical observation of the frequent development of cyanosis during the second and third decades. Campbell and Baylis (1956) found that in patients with coarctation of the aorta, the trends deduced from single measurements of the blood pressure and from serial observations tallied well. It would seem reasonable to conclude from the present findings that when the pressure is already raised in early life, it rises further with age. This has practical implications, for in a patient of, say, two years of age a pulmonary pressure of 60/30 cannot be dismissed as only moderately raised, for it is likely to rise further, probably to the stage where the shunt will become reversed.

In patients with an atrial septal defect or the common type of persistent ductus, the pulmonary pressure usually falls soon after birth and, if it rises again, this happens much later, often in the third, fourth, or fifth decades. Our findings suggest that this does not happen in patients with a ventricular septal defect and that the pulmonary pressure is high, in part at least, from birth or from a very early age.

Ventricular Pressure Differentials

(*a*) *During Diastole.* In 8 of 14 patients in whom adequate records were obtained, the lowest pulmonary capillary pressure in each patient exceeded the corresponding right ventricular diastolic pressure. The left atrial and left ventricular diastolic pressure also must, therefore, have been greater than the right ventricular. Shunting of blood through the defect is usually thought to take place during systole, accounting for the pan-systolic murmur. In the presence of these diastolic pressure differences a left-to-right shunt must be present in diastole, despite the absence of a murmur, as it seems unlikely that the defect can be closed in this phase of the cardiac cycle.

(*b*) *During Systole.* The ventricular septal defect brings the lesser circulation into direct contact with the ventricle in which the pressure normally tends to rise with the years. The fact that the right ventricular pressure may remain normal shows that the pressure differential may remain normal in spite of the defect, but this can happen only if it is small. Several authors have spoken of equalized pressures in the two ventricles and we wish to examine the evidence for this. It is unusual for the catheter to pass through the defect to the left ventricle but a measure of systemic pressure was obtained during catheterization in 32 patients with pulmonary hypertension (Table VI). The pressure in the left ventricle was recorded twice and in the aorta three times. The pressure in the brachial (or femoral) artery was recorded directly in 10 patients and was measured by sphygmomanometry in the remaining 17. The conclusions that can be drawn from observations as heterogeneous as these are somewhat limited, especially as the time elapsing between the measurement of pulmonary and systemic pressures varied greatly. The frequency with which the pulmonary pressure appeared to exceed the systemic shows the effect of differences in timing and techniques, for it is unlikely that this was really the case.

Nevertheless, comparison of pulmonary and systemic pressures does reveal one noteworthy feature. The difference was never greater than 32 mm.: in over three-quarters of the acyanotic patients the pulmonary systolic pressure was within 20 mm. of the systemic and in almost half it was within 10 mm. As in some cases it appeared to *exceed* the systemic pressure by as much as 20 mm. we cannot accept all the differences in the other direction as significant. In most large defects, therefore, the pressure differential is small and the shunt can be reversed by a slight rise in pulmonary arterial pressure.

The Rise of Normal Systemic Pressure with Age. It is not easy to find an accepted standard for the rise of blood pressure from infancy to old age, especially as many series deal with school children only and others with adults only. For children we have used average figures from various sources and for adults those of Hamilton *et al.* (1954).

The systolic blood pressure rises in an almost linear relationship with age up to about 15 years, 2·3 mm. a year, and thereafter less steeply, about 0·7 mm. a year. The diastolic rise is similar but smaller, 1·2 mm. a year below 15 and 0·4 mm. after. These figures show that the normal rise in the systemic circuit and the rise in the pulmonary circuit in our patients are of the same order. However, the right ventricular systolic pressure must rise more than the left in those patients who become cyanotic. In our cases it rose 1·3 mm. a year and this is more than the rise in systemic pressure after 15 and may explain the liability to develop cyanosis after this age.

Pulmonary Arteriolar Resistance

There is no tendency for the normal adult pulmonary arterial pressure to increase with age and Kjellberg *et al.* (1955) have shown that in 13 normal children its level was about the same as in adults. Brotmacher and Deuchar (1956) have adduced evidence that the cardiac index is about the same in children and adults. It would seem likely, therefore, that the pulmonary resistance *index* (which we have used so that children and adults could be compared) does not change significantly as a normal subject grows older.

We have found in our cases that the resistance index tends to increase with age (Fig. 8). It was normal in over one-third of those with pulmonary hypertension under 20 but in only one of those over 20 years. The cyanotic patients had higher resistances than the acyanotic, but there was some overlapping.

The left-to-right shunt and the pulmonary blood flow per unit of surface area were measurable in 51 patients, who in Table VII have been divided into the groups we have suggested except that

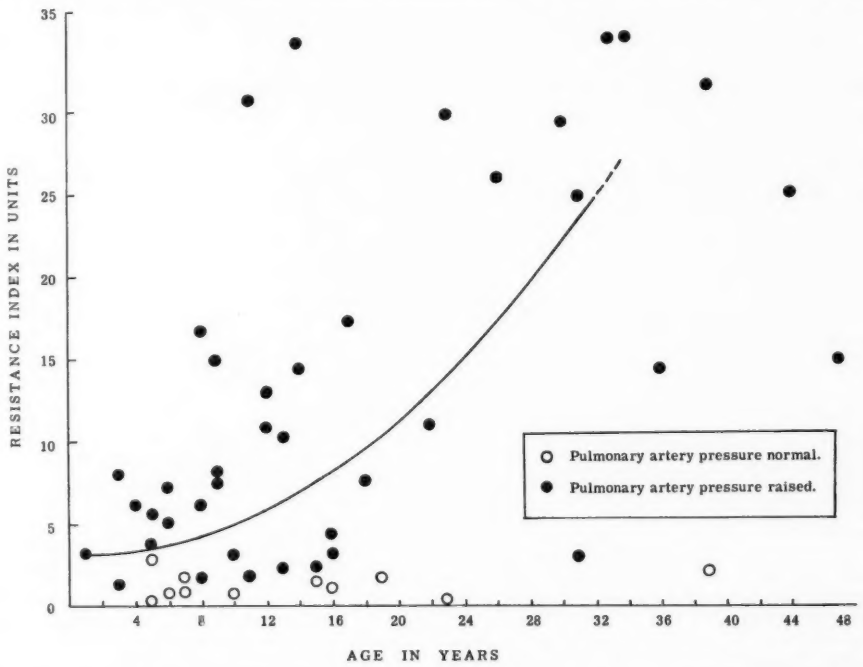


Fig. 8.—The relationship of the pulmonary arteriolar resistance to age. The mean resistance index rises with age slowly at first and more steeply during and after the second decade. Exceptionally, it may remain normal in patients over twenty or may be somewhat raised in young children before they are five. The estimated relationship is shown approximately by the curved line.

TABLE VII

RELATIONSHIP OF PULMONARY ARTERIOLAR RESISTANCE TO SHUNTS AND CYANOSIS

	Group	Pulmonary arteriolar resistance index (units)	No. of cases	Mean age	Left-to-right shunt (L./sq. m./min.)		Number with arterial O_2 saturation under 90%
					Mean	Range	
Normal P.A. pressure ..	1	3 or below	7	14·0	2·4	1·0– 4·5	0
	2	3 or below	4	13·2	8·1	6·6–10·4	0
Raised P.A. pressure ..	3	6 or below	13	10·8	11·5	4·2–20·4	0
	4	6·1–12	10	10·4	3·0	1·4–6·0	1
	5a	12·1–18	7	20·6	1·7	0–3·1	5
	5b	Above 18	10	28·5	0·6	0–1·2	10

in this instance the decision has rested only on the pulmonary arteriolar resistance. Pulmonary hypertension, even in the hyperkinetic group, is not determined solely by the size of the left-to-right shunt, for those in Group 3 did not always have larger left-to-right shunts than those with normal pulmonary pressures.

Increase in the pulmonary resistance is associated with progressive diminution in the size of the left-to-right shunt and the development and progressive increase of the right-to-left shunt (Table VII). The groups overlap to some extent: for example, some patients in Group 4 had a larger left-to-right shunt and less arterial desaturation than others in Group 5a. This overlapping emphasizes the absence of any clear cut division between cyanotic and acyanotic cases of ventricular septal defect.

In patients with pulmonary hypertension, the tendency of pulmonary resistance to rise with the years is shown again by the greater average age of the high resistance cases (Group 5). In contrast, the patients with normal pressures are, as a group, older than those with hyperkinetic pulmonary hypertension (Group 3) or with a moderate rise of pulmonary resistance (Group 4). The pulmonary pressure is therefore not very likely to become high as a late complication in patients where it is normal.

Wood *et al.* (1954) state that " high pulmonary vascular resistance does not develop over the years but is determined shortly after birth." In our view, the pulmonary pressure is usually high from birth: at first the rise is mainly hyperkinetic, but as the years pass the pulmonary arteriolar resistance gradually rises, reducing the left-to-right shunt and causing a right-to-left shunt. Blount *et al.* (1955) also concluded that the pulmonary arteriolar resistance increases with age.

CHANGES OBSERVED IN THE INDIVIDUAL PATIENT OVER THE YEARS

Since most of this was written, three patients have been recatheterized after an interval of about seven years. The first showed all the changes that we have deduced from the general study, but the second and third still showed very little change.

When he was 5, a boy had a pulmonary flow of 7·1 litres a minute with a left-to-right shunt of 5·6 and a right-to-left shunt of 0·6 litres. Seven years later he was more cyanotic but not much more disabled: his pulmonary flow was now less than the systemic, the left-to-right shunt was greatly reduced, and the right-to-left shunt was large enough to have reduced the arterial O_2 saturation from 90 to 67 per cent. When 5, his P.A.P. was 88/50 against a clinical systemic pressure of 100/70, and when he was 12 it was 120/65 against a systemic pressure 110/80. The pulmonary pressure had risen moderately but the resistance had risen greatly, from 8 to 23 units (Case 19, Table VI).

The second had a large left-to-right shunt when he was 3½ with a raised pulmonary pressure, 55/27. When 10, he was still acyanotic but the pulmonary flow was relatively smaller, 2·6 times instead of 3·7 times the systemic flow: there was hardly any change in the pulmonary pressure or in the pulmonary arteriolar resistance (Case 15).

The third had an enormous pulmonary flow of about 24 litres a minute when she was 11, with a P.A. pressure of 98/40, a rise that was entirely hyperkinetic. Seven years later there was little change. The systemic systolic pressure had been 17 mm. higher than the pulmonary but now the difference was hardly significant: the resistance index had risen from 1·8 to 3·2 units. On both occasions she was acyanotic and remained so on exertion (arterial oxygen 99 and 94%) (Case 29).

Increase in Size of Defects

We do not know whether ventricular septal defects increase in size *pari passu* with the patient's growth, but there was some evidence for this from the necropsy series of Selzer (1949). In general, they are very similar anatomically to the defects in Fallot's tetralogy and the conclusions of Brinton and Campbell (1953) and subsequent experience suggests that these latter defects increase in size. For example, in 16 cases, aged between 4 and 12, the mean diameter of the defect was 1·1 cm. and in 8 cases between 17 and 36, it was 1·8 cm. Presumably the death rate is heavier among those with a larger defect, so that if in the survivors it did not become larger with growth one would expect the older patients to have smaller defects. Whether the defect enlarges in the same proportion as the heart generally is less certain. Some children seem to adjust to their defect better as time goes on and this might be because it has grown less than the rest of the heart. For example, one boy, aged 10, seemed unlikely to survive his first three winters and was frequently in hospital with pulmonary congestion, but has been much better since (Case 15). He has recently been catheterized a second time and the shunt, relatively to his size, is less than it was seven years before.

Summary and Conclusions

This paper is based on 75 patients in whom the diagnosis of ventricular septal defect was accepted after cardiac catheterization, regardless of whether the patient was cyanotic or acyanotic. Another 100 in whom the diagnosis rested on clinical grounds alone have been used in considering the age and sex incidences.

Nearly three-quarters of all the patients were under 20 years of age, but the cyanotic patients were more equally distributed through the first four decades, showing that patients become cyanotic throughout this period.

Although the sex incidence is equal, there were far more women than men over 20, and among the cyanotic the female were older than the male patients. The prognosis in boys and men, therefore, appears to be more serious than in girls and women.

Some of the clinical features are reviewed shortly. We think the terms maladie de Roger and Eisenmenger's complex have outlived their usefulness and should no longer be used, and still less the term Eisenmenger's syndrome which adds confusion instead of clarity. Classification should depend on the size and direction of the shunt and the level of the pulmonary arterial resistance.

In acyanotic patients the heart will be large if the shunt is large. In cyanotic patients, it may be large or may be normal in size when the left-to-right shunt has never been large or has ceased to be so because of the high pulmonary arterial pressure. Pulmonary regurgitation is found in one-third of the patients with pulmonary hypertension.

If the patient survives infancy, the prognosis is fairly good for fifteen years or so; but unless the defect and the shunt are small, it becomes increasingly bad thereafter, and few such patients survive to 40 years of age.

In ventricular, as opposed to atrial septal defects, the pressure may be transmitted directly from the left to the right ventricle. The pressure differential between the ventricles will be normal if the defect is small, in which case the shunt is generally less than 3·5 litres a minute, though sometimes much larger—presumably with a defect of intermediate size. Generally, however, the defect is larger and the pressure differential is small, no more than 10 or 20 mm.; this enables the heart to maintain a reasonable systemic flow in spite of the large shunt.

The right ventricular and pulmonary arterial pressures are already high in small children, probably from birth. Although at first the rise is generally hyperkinetic, subsequently it is due partly to the natural rise in left ventricular pressure but mainly to the pulmonary arteriolar resistance, which increases with age and becomes the most important factor.

At some stage, often in the third decade but sometimes earlier and sometimes later, the right ventricular pressure may rise rather faster than the left so that the left-to-right shunt becomes much smaller, a right-to-left shunt develops, and the patient becomes cyanotic. These changes are adequately accounted for by the levels of the right and left ventricular pressures, and there is no need to invoke any pulmonary factor to explain the cyanosis or to place much importance on the anatomical position of the aorta. We are, therefore, in agreement with Selzer (1953) and Blount (1955) in treating the acyanotic and cyanotic cases as a single group. The exact stage at which these changes make successful operation for closing the ventricular septal defect impossible will need precise definition, but it may be relatively early.

References

Baylis, J. H., Campbell, M., Gilmore, H. R., and Hudson, R. (1955). *Guy's Hosp. Rep.*, **104**, 114.

Becu, L. M., Fontana, R. S., Du Shane, J. W., Kirklin, J. W., Burchell, H. B., and Edwards, J. E. (1956). *Circulation*, **14**, 349.

Blount, S. G., Jr., Mueller, H., and McCord, M. C. (1955). *Amer. J. Med.*, **18**, 871.

Bowers, D., Burchell, H. B., and Wood, E. H. (1955). *Proc. Mayo Clin.*, **30**, 261.

Brinton, W. D., and Campbell, M. (1953). *Brit. Heart J.*, **15**, 335.

Brotmacher, L., and Campbell, M. (1958). *Brit. Heart J.* To be published.

——, and Deuchar, D. C. (1956). *Clin. Sci.*, **15**, 441.

Brown, J. W. (1955). *Congenital Heart Disease*. London. Staples Press.

Burchell, H. B., Taylor, B. E., Pollack, A. A., DuShane, J. W., and Wood, E. H. (1948). *Proc. Mayo Clin.*, **23**, 507.

Campbell, M. (1954). *Brit. Heart J.*, **16**, 275.

—— (1955). *Brit. Heart J.*, **17**, 526.

——, and Baylis, J. H. (1956). *Brit. Heart J.*, **18**, 475.

——, Neill, C., and Suzman, S. (1957). *Brit. med. J.*, **1**, 1375.

——, and Thorne, M. G. (1956). *Brit. Heart J.*, **18**, 95.

Dexter, L., Haynes, F. W., Burwell, C. S., Eppinger, E. C., Sosman, M. C., and Evans, J. M. (1947). *J. clin. Invest.*, **26**, 561.

Griffin, G. D. J., and Essex, H. E. (1951). *Surg. Gynæc. Obst.*, **92**, 325.

Hamilton, N., Pickering, G. W., Roberts, J. A. F., and Sowry, G. S. C. (1954). *Clin. Sci.*, **13**, 11.

Handelsman, J. C., Bing, R. J., Campbell, J. A., and Griswold, H. E. (1948). *Bull. Johns Hopk. Hosp.*, **82**, 615.

Joly, F., Carlotti, J., and Scot, J. R. (1951). *Arch. Mal. Cœur.*, **7**, 602.

Kjellberg, S. R., Mannheimer, E., Rudhe, U., and Jonsson, B. (1955). *Diagnosis of Congenital Heart Disease*. Chicago.

Laubry, C., and Pezzi, C. (1921). *Traité des Maladies Congénitales du Cœur*. J. B. Baillière et fils, Paris.

Laubry, C., Routier, D., and Soulié, P. (1933). *Rev. Méd. Paris*, **50**, 439.

Mannheimer, E., Ikkos, D., and Jonsson, B. (1957). *Brit. Heart J.*, **19**, 333.

Marquis, R. M. (1950). *Brit. Heart J.*, **12**, 265.

Roger, H. (1879). *Bull. Acad. Méd.*, **8**, 1074.

Routier, D., Soulié, P., and Bernal, P. (1949). *Arch. Mal. Cœur*, **42**, 765.

Selzer, A. (1949). *Arch. intern. Med.*, **84**, 798.

—— (1954). *J. Amer. med. Ass.*, **154**, 129.

——, and Laquer, G. L. (1951). *Arch. intern. Med.*, **87**, 218.

Soulié, P., Voci, G., Carlotti, J., and Joly, F. (1953). *Arch. Mal. Cœur*, **46**, 481.

Taussig, H. B. (1947). *Congenital Malformations of the Heart*. New York, Commonwealth Fund.

Wood, P. (1950). *Brit. med. J.*, **2**, 639 and 693.

—— (1954). *Brit. med. J.*, **1**, 1051 and 1113.

—— (1956). *Diseases of the Heart and Circulation*. 2nd ed. Eyre and Spottiswode, London.

—— (1957). Personal communication.

——, Magidson, O., and Wilson, P. A. O. (1954). *Brit. Heart J.*, **16**, 387.

EVALUATION OF DYE INJECTION METHODS IN CONGENITAL HEART DISEASE

BY

WALTHER FALHOLT AND JØRGEN FABRICIUS

From the Medical Clinic B, Rigshospitalet (Physician-in-Chief, Professor Erik Warburg), University of Copenhagen Denmark

Received August 30, 1957

Obtaining dye dilution curves after injection of Evans blue dye into the circulation has been greatly facilitated through the introduction of direct recording colorimeters. These allow for continuous sampling of blood from a systemic artery or through a cardiac catheter, and registration of the dye curve either photographically or by a direct writing system (Friedlich *et al.*, 1950; Shadle *et al.*, 1953; and Falholt and Kaiser, 1955).

The colorimeters have the advantage over ear oximeters, constructed for the same purpose, that concentrations of dye are registered more centrally in the circulation from a brachial or femoral artery, so that distortion of the dye curves due to laminar flow in the smaller arteries and capillaries is avoided. Further disadvantages of the ear oximeters hitherto constructed are erroneous deflections due to instability in the fixation of the ear-piece, and deflections independent of the momentary dye concentration caused by spontaneous fluctuations in oxygen saturation of the blood. In acyanotic cases of congenital heart disease this cause of error in dye concentrations measured may be diminished by letting the patient inspire pure oxygen (Swan *et al.*, 1953), but in cyanotic cases this attempt at correction is not permissible.

The dye colorimeter used in the present observations automatically corrects for changes in oxygen saturation of the blood sampled (Falholt and Kaiser, 1955).

METHODS

In all cases of congenital heart disease in which dye dilution curves were obtained, this procedure was performed at the end of cardiac catheterization, after the diagnosis was established. Evans blue dye, T-1824, was injected through the cardiac catheter, when the tip of the catheter was at the position in the heart or pulmonary artery, where the injection of dye was expected to give a dilution curve most characteristic of the particular malformation. The amount of dye injected was roughly estimated from the size of the patient, and the size and direction of the shunt, as determined from the catheter findings, and 5 to 30 mg. of dye were injected as rapidly as possible. The catheter was filled with dye 3 to 5 minutes before the injection, so that the actual amount of dye entering the circulation during the registration of the dye curve was identical with that leaving the syringe. In this way the necessity of correcting for the dead space in the catheter was avoided.

Puncture of the brachial or femoral artery was performed immediately before the final injection of dye, with a needle connected with a 15 cm. long plastic tube leading to the dye colorimeter. The dye curves were registered on 12 cm. wide paper, passing with a speed of 1 cm. per second through the direct writing system of the apparatus.

The oxygen saturation of blood samples taken during cardiac catheterization was determined by the Brinkman-Zijlstra (1949) hæmoreflector and the van Slyke method. Pressure measurements were performed by the electrical condenser manometer of Hansen (1949), a development of the manometer originally designed by Buchtal and Warburg (1943). The oxygen consumption was estimated according to Boothby

et al. (1936). Calculations of the flows and shunts were made according to Bing *et al.* (1947). The results obtained in the cases illustrated by the figures are seen in Table I.

TABLE I

HÆMODYNAMIC DATA OF THE PATIENTS SHOWN IN THE FIGURES

Diagnosis	Fig. 1	Fig. 2	Fig. 3	Fig. 4	Fig. 5	Fig. 6	
	Fallot's tetralogy	Pulmonary stenosis with A.S.D.	Fallot's tetralogy	A.S.D.	Pulmonary stenosis	A.S.D & A.P.V.D.	
						Before op.	After op.
O_2 consumption (c.c./min.) ..	129	176	180	264	258	146	146
Systemic flow; lit./min. ..	7·6	5·9	4·4	6·5	4·5	2·5	3·4
Pulm. flow: lit./min.	2·9	2·9	3·2	16·5	4·3	6·1	3·4
Effective flow: lit./min... ..	2·9	2·9	3·2	6·5	4·3	2·5	3·4
L. to R. shunt	0	0	0	10·1	0	3·6	0
R. to L. shunt	4·7	2·9	1·2	0	0	0	0

RESULTS AND DISCUSSION

Cyanotic Cases of Congenital Heart Disease

The right-to-left shunt causing the cyanosis may be due to defects in the atrial or ventricular septa, to an overriding or transposed aorta, or to an abnormal communication between the great vessels, that is aorto-pulmonary defect or a patent ductus with pulmonary hypertension and partial or total reversal of the flow through the duct. Naturally the presence of a right-to-left shunt will result in a dye curve different from that found normally, when dye is injected at a place correctly chosen in relation to the site of the shunt: the larger the shunt the more pronounced this difference will be. Fig. 1 illustrates a normal dye curve (above) and one obtained in a case of Fallot's tetralogy with a considerable right-to-left shunt (below). The dye in this case was injected into the right atrium. It may be seen, that shortly after the injection an initial hump is obtained due to dye that has passed through the over-riding aorta, and 7 seconds later a further increase in concentration of

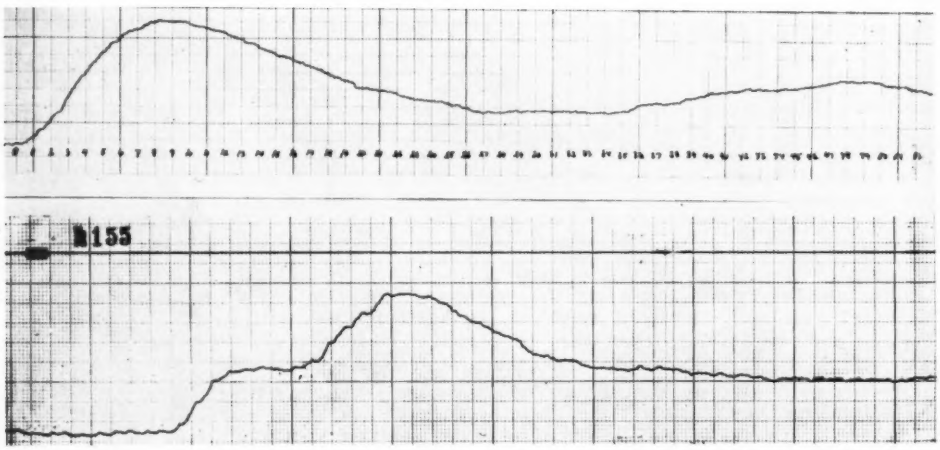


FIG. 1.—Dye dilution curves. *Upper curve* from a normal subject; *lower curve* from a case of Fallot's tetralogy with a considerable right-to-left shunt, resulting in an initial hump on the dye curve. Paper breadth 12 cm., time between the heaviest lines 5 seconds. 15 mg. of dye were injected into the right atrium.

dye occurs, due to dye that has passed the lungs and left side of the heart. A similar dye curve will be found in any of the heart diseases mentioned with a right-to-left shunt, provided that the dye is injected into the blood stream before the shunt. The initial hump, however, will be more or less pronounced according to the size of the shunt.

It has been suggested (Swan and Wood, 1953), that localization of the defect can be established by injection of the dye into the pulmonary artery, the right ventricle, and right atrium, successively. This may be true in certain instances, as when making the differential diagnosis between Eisenmenger's complex and a patent ductus with a reversed shunt. This differential diagnosis, however, can practically always be established by cardiac catheterization alone (generally by direct catheterization of the duct which in this case is always wide, or of the overriding aorta). It is our experience that the dye injection method is unreliable when used for distinguishing between an atrial septal defect in combination with pulmonary stenosis and a ventricular septal defect in Fallot's tetralogy.

Fig. 2 illustrates a case of pulmonary stenosis and atrial septal defect, in which the dye was injected into the right ventricle and blood sampled from a femoral artery. In spite of the injection of the dye into the right ventricle, an initial hump, similar to that found in cases of Fallot's tetralogy,

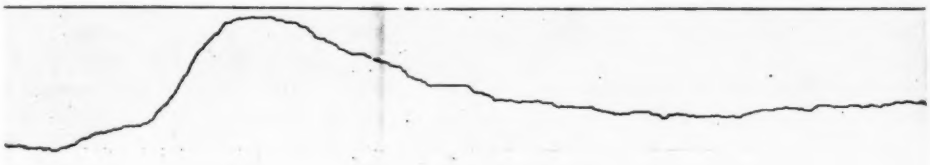


FIG. 2.—Dye dilution curve from a case of pulmonary stenosis with a defect of the atrial septum. The dye was injected through a cardiac catheter into the right ventricle and blood was sampled from a femoral artery (20 mg. of dye injected).

was obtained. Catheterization findings gave no evidence of overriding of the aorta, ventricular septal defect, nor abnormal communications between the great vessels. The pressure in the right ventricle was 182/–3 and in the systemic arteries 110/80 mm. Hg, which excludes the diagnosis of Fallot's tetralogy (Gøtzsche *et al.*, 1952). The initial hump found in this case is explained as the result of a slight tricuspid incompetence, resulting in passage of dye from the right ventricle into the right atrium, and further on through the atrial septal defect via the left heart to the aorta, before the dye passing through the lungs has reached so far. We, therefore, do not use the dye injection method diagnostically in cases of Fallot's tetralogy and pulmonary stenosis with a defect of the atrial septum, as we consider the results obtained by cardiac catheterization and possibly angiocardiography sufficient and more reliable.

In cases of congenital heart disease accompanied by very small right-to-left shunts, the interpretation of the dye curve is even more questionable. A case of Fallot's tetralogy with a rather small left-to-right shunt is seen in Fig. 3.

FIG. 3.—Dye dilution curve from a case of Fallot's tetralogy with a rather small right-to-left shunt. The initial hump is only slightly indicated.

Such dye curves have been used for estimation of the right-to-left shunt in congenital heart disease (Swan *et al.*, 1953). The formulae given are based upon so many assumptions and the introduction of correction factors, which are not even constant from one case to another, that these calculations cannot be considered of any practical value. The curves are composed of portions of dye passing through the defect and portions passing the normal way. As one can not distinguish between these portions a mathematical analysis of the curves is impossible. Direct visual inspection of the dye curves, however, may give a rough estimate of the magnitude of the shunt.

Acyanotic Cases of Congenital Heart Disease

This group of congenital heart diseases includes those with a pure left-to-right shunt and those without any shunt. The dye injection method cannot be expected to be of value in cases with no shunt, except by excluding the presence of any shunt. Small shunts, however, cannot be diagnosed reliably by this method.

Broadbent and Wood (1954) maintained that cases of left-to-right shunt of sufficient magnitude show a typical pattern of the dye curve. The characteristics are: (1) an appearance time (time between injection of the dye and the beginning of the upstroke of the dye curve) and a build-up-time (duration of the upstroke) of normal duration; (2) a maximum of dye concentration that is lower than would be anticipated in a normal dye curve; (3) an elongation of the disappearance slope (downstroke of the dye curve); and (4) absence of the peak indicating recirculation of dye. (Note the secondary peak on the normal curve in Fig. 1.) This configuration of the dye curve was found in all cases of more pronounced left-to-right shunt in atrial septal defect, abnormal pulmonary venous drainage to the right side of the heart, ventricular septal defect, and patent ductus. This characteristic pattern of dye curve, therefore, is of no differential-diagnostic value, but only indicates the presence of a left-to-right shunt (Fig. 4).

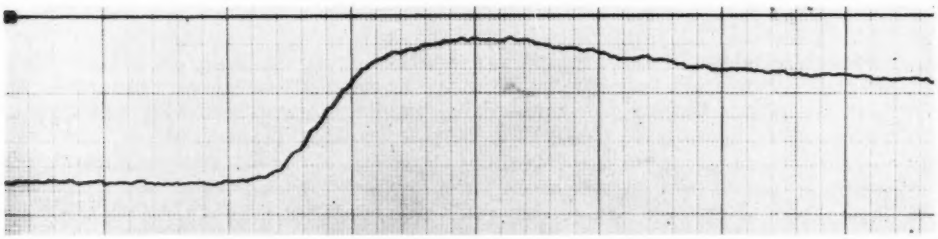


FIG. 4.—Dye dilution curve from a case of atrial septal defect with a large left-to-right shunt. (20 mg. of dye injected.)

Considering the first point: the appearance time is dependent upon the velocity of blood flow and the volume of blood between the site of injection and registration. The appearance time, therefore, is highly variable from one case to another, especially when dye is injected into an antecubital vein instead of through a cardiac catheter into the heart. The build-up-time will be discussed later. Because of the shunting of blood from left to right it is quite logical that the maximum of the dye curve will be relatively small, as blood and dye are steadily recirculating in the lesser circulation, and dye therefore only gradually reaches the aorta. This is also an explanation of the slow decrease of dye concentrations on the dilution curve. Absence of the peak due to recirculation is understandable, as systemic recirculation is diminished because of the shunting of blood from left to right, and the prolonged dilution of dye. Absence of the recirculation peak is not pathognomonic for left-to-right shunts.

The configuration of the dye curve described may be found in certain other conditions than those mentioned, such as low cardiac output, congestive heart failure, and even in pulmonary stenosis with no left-to-right shunt with low cardiac output or large residual volume in the right

ventricle (Fig. 5). Broadbent and Wood have, therefore, suggested that the ratio of the disappearance time to the build-up-time (that is duration of downstroke/duration of upstroke) as a more reliable expression of a left-to-right shunt than the disappearance time alone. As, however, the build-up-time is normal in cases of left-to-right shunt (i.e. independent of the presence of a left-to-right shunt) and, furthermore, the duration of the upstroke of the dye curve is dependent upon the volume of blood in the central veins (the dye was injected into an antecubital vein), the volume of blood in the heart and lungs, and not least the rate of injection, the value of this ratio seems doubtful.

As in any case cardiac catheterization is necessary for localizing the abnormal arterio-venous communication and gives sufficient and reliable information for calculation of the shunts with fair exactness by the Fick principle (Bing *et al.*, 1947), the dye injection method can hardly be considered of any diagnostic value in cases of acyanotic heart disease.

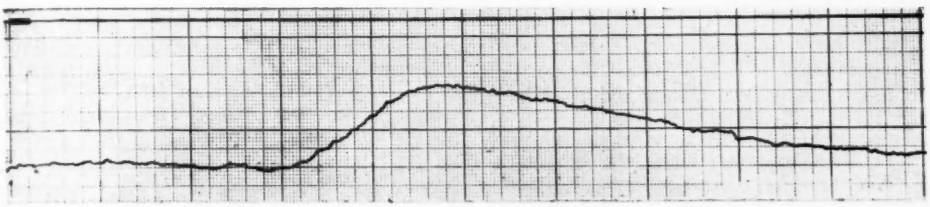


FIG. 5.—Dye dilution curve from a case of pure pulmonary stenosis. The curve shows the same pattern as in cases of congenital heart disease with a left-to-right shunt. Time and duration of dye injection (20 mg.) is marked in the upper left corner.

It is our experience, however, that the dye injection method used on a comparative basis may give important information concerning the physiological conditions, especially when judging the result of attempts at surgical correction of cardiac malformations. This is illustrated in Fig. 6. The dye curves shown were obtained in a patient with atrial septal defect and two pulmonary

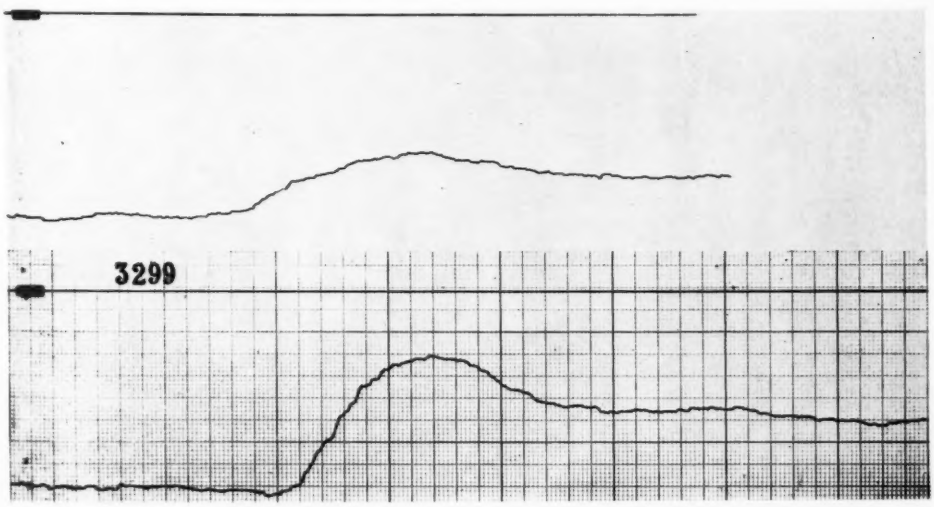


FIG. 6.—Dye dilution curves obtained in a case of atrial septal defect and two pulmonary veins draining abnormally into the right atrium, before (upper curve) and after operation by Biörk's method (lower curve). Further explanation is found in the text.

veins draining abnormally the right atrium. The upper curve was obtained before operation: 15 mg. of Evans blue dye was injected through a cardiac catheter into the left atrium, and blood was sampled from the femoral artery. After the operation (lower curve) 10 mg. of dye were injected into the right atrium: in spite of the smaller quantity injected and the injection into the right instead of the left atrium, a considerably higher maximal concentration, a steeper dilution, and an indication of a recirculation peak were obtained as evidence of satisfactory result of the operation.

Summary

The introduction of whole blood colorimeters for continuous registration of Evans blue dye concentrations has made it much easier to obtain dye dilution curves in human subjects.

Our attempt at using the dye injection method diagnostically in congenital heart disease has been disappointing, and only exceptionally does it give information that was not obtained by cardiac catheterization or angiocardiography. The dye injection method, however, is a valuable and easy method of judging the circulatory conditions before and after operations for congenital heart disease associated with left-to-right or right-to-left shunts.

References

Bing, R. J., Vandam, L. D., and Gray, Jr., F. D. (1947). *Bull. Johns Hopk. Hosp.*, **80**, 107.
Boothby, W. M., Berkson, J., and Dunn, H. L. (1936). *Amer. J. Physiol.*, **116**, 468.
Brinkman, R., and Zijlstra, W. G. (1949). *Arch. Chir. Neerland*, **1**, 177.
Broadbent, J. C., and Wood, E. H. (1954). *Circulation*, **9**, 890.
Buchtal, F., and Warburg, E. (1943). *Acta Physiol. Scand.*, **5**, 55.
Falholt, W., and Kaiser, E. (1955). *Circulation Res.*, **3**, 469.
Friedlich, A., Heimbecker, R., and Bing, R. J. (1950). *J. Applied Physiol.*, **1**, 12.
Gøtzsche, H., Hansen, A. T., and Eskildsen, P. (1952). *Acta med. Scand., Suppl.*, 266, 445.
Hansen, A. T. (1949). *Pressure Measurements in the Human Organism.* Teknisk Forlag, Copenhagen.
Shadle, O. W., Ferguson, T. B., Gregg, D. E., and Gilford, S. R. (1953). *Circulation Res.*, **1**, 200.
Swan, H. J. C., Zapata-Diaz, J., and Wood, E. H. (1953). *Circulation*, **8**, 70.
—— and Wood, E. H. (1953). *Proc. Staff Meet. Mayo Clin.*, **28**, 95.

DISAPPEARANCE OF PATHOLOGICAL Q WAVES AFTER CARDIAC INFARCTION

BY

M. P. PAPPAS*

From the Department of Cardiology, the Middlesex Hospital

Received June 6, 1957

Experimental ligation of a branch of a coronary artery has shown that the affected part of the myocardium passes through a number of stages, namely ischæmia, injury, and necrosis, the latter producing Q or QS waves in electrocardiographic leads taken over the necrosed area. If this dead area is transmural, it does not react to the stimulus of contraction and leads from points over it simply reflect the intracavity potential. The earlier stages, ischæmia and injury, are responsible for changes in the part of the electrocardiogram that is due to repolarization, i.e. the R–T segment and T

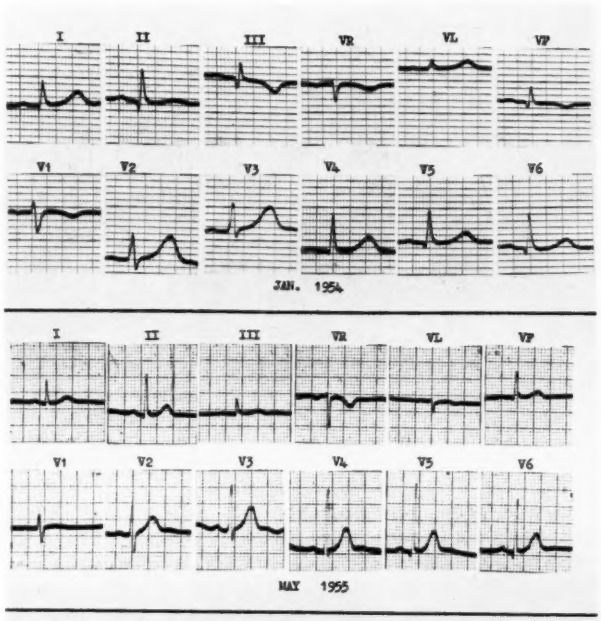


FIG. 1.—Cardiogram showing posterior cardiac infarction (January, 1954). In the lower tracing (May, 1955) abnormal Q and T waves have disappeared and the curve is within normal limits.

* Present address: Laikon Hospital, University of Athens, Greece.

wave. After ligation of the artery the R–T segment and T wave changes are reversible whereas the abnormal Q is permanent. In clinical cases, the cardiogram shows similar changes. After the acute phase of the infarction, the QRS–T complex gradually evolves to its permanent form; in many uncomplicated cases, the R–T segment and T wave become normal, the only residual abnormality being a deep Q or QR wave in leads where previously there was an R wave.

Experience has shown that while the abnormal Q wave is usually permanent (Wallace, 1934; Vander Veer and Edwards, 1939), rarely it may contract to normal dimensions, in which case the whole ventricular complex is normal. Little has been written on this point and few cases have been reported in which the cardiogram has returned to normal after the acute phase of a transmural infarction had subsided.

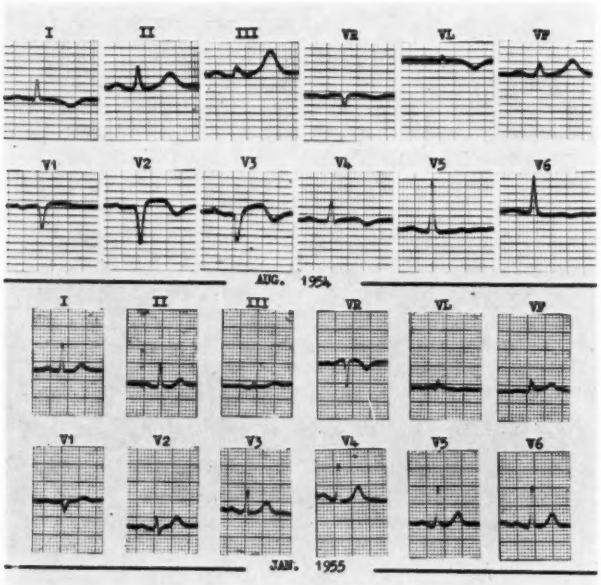


FIG. 2.—Signs of antero-septal infarction with ischæmic changes in the left chest leads were present in August, 1954. Five months later (January, 1955) the curve was normal.

Bohning and Katz (1938) followed up 200 cases of coronary occlusion over a period of three years and found only one in which the Q wave of a posterior infarction disappeared 18 months after the acute phase. Goldberger (1953) is of the opinion that an abnormal Q wave might occasionally diminish in size so that it could not be distinguished from a normal one and reports a case of posterior infarction in which it returned to normal dimensions in III and aVF after the acute episode, but emphasizes that it usually remains abnormal through life (Goldberger, 1955). Levine (1951) also believes that on rare occasions the abnormal Q wave disappears. On the other hand, Coelho *et al.* (1950) in a follow up of 320 cases of cardiac infarction do not mention even one instance in which the cardiogram returned to normal, no matter how the clinical condition had improved. The very few published instances of disappearance of abnormal Q waves related to posterior infarctions; no example involving an anterior infarction has been reported so far.

In order to find out how often the QRS complex can revert to normal after healing of the necrosed area, we reviewed the cardiograms of 742 cases of cardiac infarction occurring between 1949–55 which were followed up in the Department of Cardiology of the Middlesex Hospital and

discovered 14 cases (1·9%) that seemed to have the necessary criteria. All were men between the ages of 49 and 66; six were above 55 and eight below, the average being 54 years. There was a short history of anginal pain before the infarction in all patients except two who had complained of pain for six months and two years respectively. The blood pressure in the majority was within normal limits. Nine patients had an antero-septal infarction, four had posterior infarction, and one had both. In one, the cardiographic signs of acute necrosis disappeared within a month. In all the others, reversion to normal took place between 2 and 18 months. Illustrative cases are shown in Fig. 1–4.

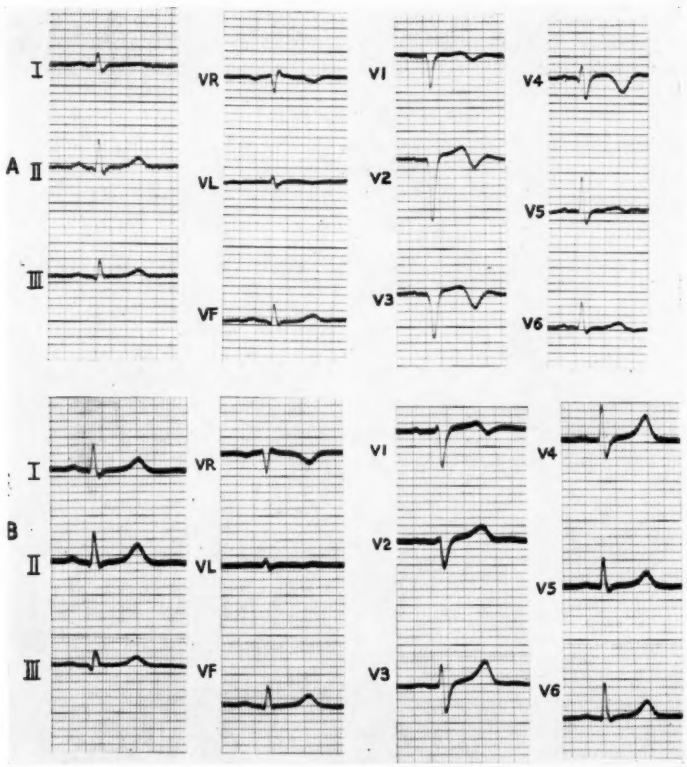


FIG. 3.—(A) Typical changes of antero-septal infarction are seen in leads V1–V4 in tracings taken in March and April, 1952. (B) In August, 1954, the cardiogram is normal.

When a pathological Q wave in III and aVF disappears or gives place to a small q of normal dimensions it is presumed that the scarred area has become too small to be detected by the limb leads in view of the wide angle subtended between these leads which must inevitably include a large portion of healthy myocardium. It is known that high posterior infarctions may not be detected by any of the conventional 12 leads. Shrinkage of the fibrous tissue in the posterior infarcts of the present series may have resulted in a higher localization than usual. Consequently a small q was recorded in leads III and aVF. But in two (Cases 6 and 8), the abnormal Q waves were replaced by small r waves in the same leads (III and aVF) leaving no evidence of a previous posterior infarction.

Holzmann (1952) points out that sometimes an abnormal Q wave disappears when a second infarction appears. In the case of Bohning and Katz (1938) the Q of a posterior infarction was abolished when, after one and a half years, a new anterior infarction took place. In Cases 3 and 8 of our series the signs of an anterior infarction disappeared a few months after a fresh posterior infarction. Probably as the new infarction develops, a slight rotation of the heart masks the exact localization of the previously infarcted area. Levy and Hyman (1950) say the signs of a healed posterior infarction are occasionally difficult to differentiate from a normal tracing in a patient whose heart is in a horizontal, slightly clockwise-rotated position.

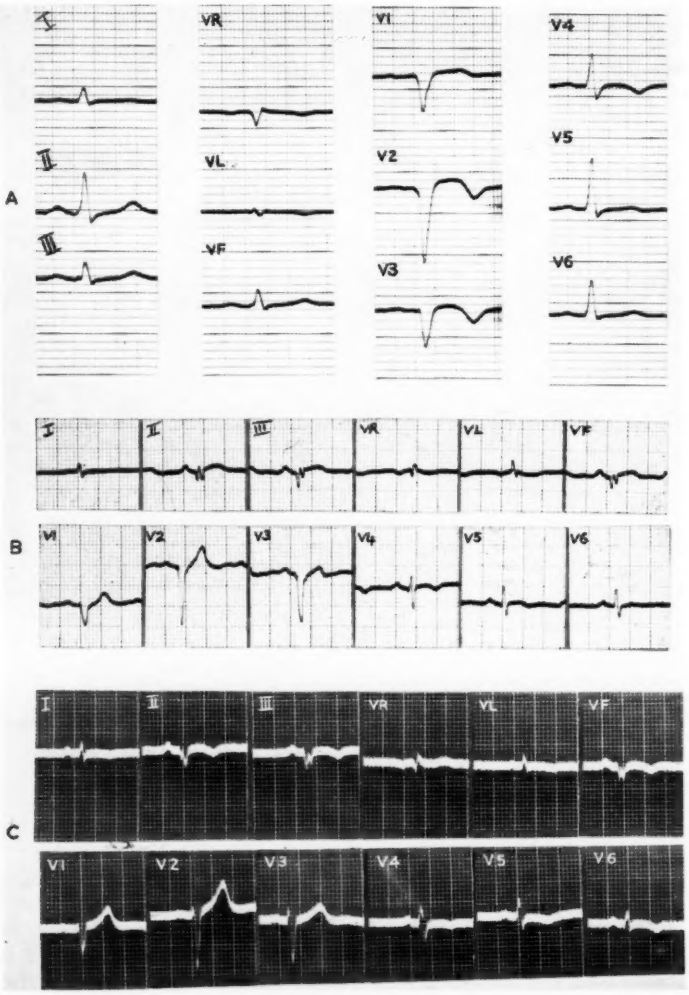


FIG. 4.—(A) Antero-septal infarction in January, 1953. (B) In February, 1955, posterior infarction has developed, with typical changes in leads II, III, and VF, the signs of antero-septal infarction persisting. (C) By March, 1955, the signs of antero-septal infarction have disappeared, but the postero-lateral ischæmic changes still remain.

But what has been said up to now concerns only posterior infarctions. The anterior and lateral walls of the heart are explored in more detail by the præcordial leads and it is hard to believe that a necrosed area here can disappear or that the abnormal Q waves in the chest leads can be replaced by R waves. Contratto *et al.* (1939) pointed out that the characteristic signs of infarction in the chest leads never disappeared in the cases they had followed. Vander Veer and Edwards (1939) agree that reversion to normal seldom if ever occurs.

In the case of antero-septal lesions, the explanation that has been given for the disappearance of the Q waves in posterior infarctions can also apply. Probably in these infarcts as well, the healed area has contracted in a part of the septum that is not detectable from the præcordial leads and the myocardium reflected in V1–3 is activated in the normal manner. In recent septal infarctions the part of the septum responsible for the r waves ceases to contract and so a QS deflection appears in these leads. When healing is complete and the affected area has been so diminished in size that only the lower part of the septum is inert, excitation of the upper septum is virtually normal, with the result that r waves reappear in the right chest leads.

Although similar pathological changes no doubt occur during healing of antero-lateral infarcts, leads V4–7 permit such detailed exploration of excitation in this area that the changes due to even small areas of necrosis are detectable. This probably explains the absence of any case in our series with antero-lateral infarction showing subsequent reversion to normality.

The reappearance of a normal cardiogram is no doubt related to the development of collateral circulation in the dead area. The failure of such a circulation to develop might explain why in other instances of antero-septal infarction there is no reversion to normal. In the present series the coronary arteries and their branches were presumably in a relatively healthy state before the occlusion and so the collateral circulation developed fully. Prinzmetal *et al.* (1948) have proved that even in the normal heart an abundant collateral circulation exists and a sudden obstruction of a major pathway permits the opening of preformed collateral channels. Possibly this collateral circulation can develop more readily in the antero-septal part of the myocardium, and this may explain some cases we have seen in which QS waves that were present in all chest leads from V1–V5 had become normal in V–V3 after some years although V4–5 still showed QS deflection. But not all the cases can develop the same degree of collateral circulation. Hecht (1949) showed two cases of infarction of the same branch of the left coronary artery demonstrated at autopsy: in one, a few years after the acute episode, the collateral circulation was almost perfect, whereas in the other it remained very poor. Does the collateral circulation develop to such an extent in these cases as to give a normal cardiogram? We have no necropsy confirmation.

Summary

In a review of all cardiac infarctions seen in the Cardiac Department of the Middlesex Hospital between 1949–55 we have found 14 cases in which the abnormal ventricular complex of the electrocardiogram returned to normal. The infarction had been antero-septal in nine, posterior in four, and both antero-septal and posterior in one. No case of antero-lateral infarction reverted to normal.

All occurred in men with a short history of anginal pain, with the exception of two, who had angina of effort for six months and two years respectively. The blood pressure in most instances was within normal limits. The progress, in all the cases, after the infarction was satisfactory. The explanation is discussed and reasons are given for thinking that the return of the cardiogram to normal is due to the shrinkage of the healed area in a part of the myocardium not electrically detectable. A further factor may be the development of an efficient collateral circulation.

I am indebted to Dr. D. Evan Bedford for his encouragement in carrying out the present paper and to Dr. W. Somerville and Dr. E. M. M. Besterman for their criticism and advice.

References

Bohning, A., and Katz, L. N. (1938). *Arch. intern. Med.*, **61**, 241.
Coelho, E. Sousa, B.A., Bordalo, e sá, I. Barata, MI, and Maltez, J. (1950). *Arch. bras. Cardiol.*, **3**, 445.
Contratto, A. W., Robinson, R. W., and Levine, S. A. (1939). *Arch. intern. Med.*, **63**, 732.
Goldberger, E. (1953). *Unipolar Lead Electrocardiography and Vectorcardiography*. Kimpton, London.
—— (1955). *Heart Disease*. Kimpton, London.
Hecht, H. H. (1949). *Arch. intern. Med.*, **84**, 711.
Holzmann, M. (1952). *Clinical Electrocardiography*. Staples Press, London.
Levine, S. A. (1951). *Clinical Heart Disease*. Saunders, London.
Levy, L., and Hyman, A. L. (1950). *Amer. Heart J.*, **39**, 243.
Prinzmetal, M., Bergman, H. C., Kruger, H. E., Schwartz, L. L., Simkin, B., and Sobin, S. S. (1948). *Amer. Heart J.*, **35**, 689.
Vander Veer, J. B., and Edwards, J. C. (1939). *Amer. J. med. Sci.*, **197**, 663.
Wallace, A. W. (1934). *Amer. J. med. Sci.*, **188**, 498.

ELECTROCARDIOGRAPHIC DIAGNOSIS OF RIGHT VENTRICULAR HYPERTROPHY IN INFANCY AND CHILDHOOD

BY

ARTHUR HOLLMAN*

From the Montreal Childrens Hospital and the Department of Pediatrics, McGill University

Received July 21, 1957

The demonstration of ventricular hypertrophy is a routine step in the diagnosis of congenital heart disease and it is important that the accuracy of the electrocardiographic criteria for the diagnosis of ventricular hypertrophy should be known and their reliability established. Such criteria have been defined and studied extensively in adults, but less so in infants and children.

In view of the particular difficulties attending the diagnosis of right ventricular hypertrophy (R.V.H.) in the first few years of life, a particular study of this subject has been made. Criteria will be presented for this diagnosis from one month to fifteen years of age and their usefulness determined by applying them to a series of cases of congenital heart disease with autopsy proof of hypertrophy of the right ventricle. In assessing the value of the electrocardiogram in detecting ventricular hypertrophy it is believed that autopsy proof is highly desirable, since clinical and radiological findings are not necessarily reliable either in detecting hypertrophy or in distinguishing which ventricle is affected.

Previous Views of Diagnostic Criteria

Gordon and Goldberg (1951) concluded that the diagnosis of right heart strain was very difficult under the age of three years. Schaffer (1950) reported on five infants and found that serial tracings with a sequence of increasing right ventricular preponderance were valuable evidence of R.V.H. Sokolow and Edgar (1950) found that 28 out of 29 autopsy cases of R.V.H. had electrocardiographic evidence for this: but the majority of their cases were children, 14 being under the age of one year and several of their criteria would indicate the presence of R.V.H. even in normal infants and children. Goodwin (1952) examined 36 cases with presumed R.V.H., aged 3–14 years, and found the R/S ratio in V1 to be greater than 1·0 in 80 per cent of his cases and considered this to be an important diagnostic sign. This ratio may however be over 1·0 in normal children up to the age of 10 years. Veasey and Adams (1952) modified the criteria of Sokolow and Lyon (1949) for use in children: among cases of congenital heart disease they found that the R/S ratios in V1 and V5 were the most reliable indication of ventricular hypertrophy but it is not clear what values for the criteria they considered abnormal at various ages. Cabrera and Monroy (1952) distinguished between the pattern of " systolic overloading " with a high R and inverted T in V1, and " diastolic overloading " with right bundle-branch block. Ziegler (1956) found a direct correlation between the incidence of positive T waves in the right præcordial leads and the rise of right ventricular mean pressure.

Determination of the Criteria

In infancy and early childhood the right ventricle is relatively thick compared with the left, the ratio between the two at birth being 6 to 7, compared with 1 to 2 in adult life. After the age of

* Work undertaken while Bilton Pollard Travelling Fellow of University College Hospital Medical School. Present address: Hammersmith Hospital, London, W.12.

three months the left ventricle starts to become dominant and by the age of 6 years the normal left ventricular dominance of adult life is largely established, but a slow change occurs up to the time of puberty. This physiological right ventricular dominance gives rise to electrocardiographic changes that are similar to those of right ventricular hypertrophy in adult life. The R.V. dominance at birth and its subsequent gradual involution are clearly shown in the R/S ratios in leads V1, V5, and aVR at different ages (Fig. 1). The R/S in V1 averages 3·7 from one to three months of age, falling

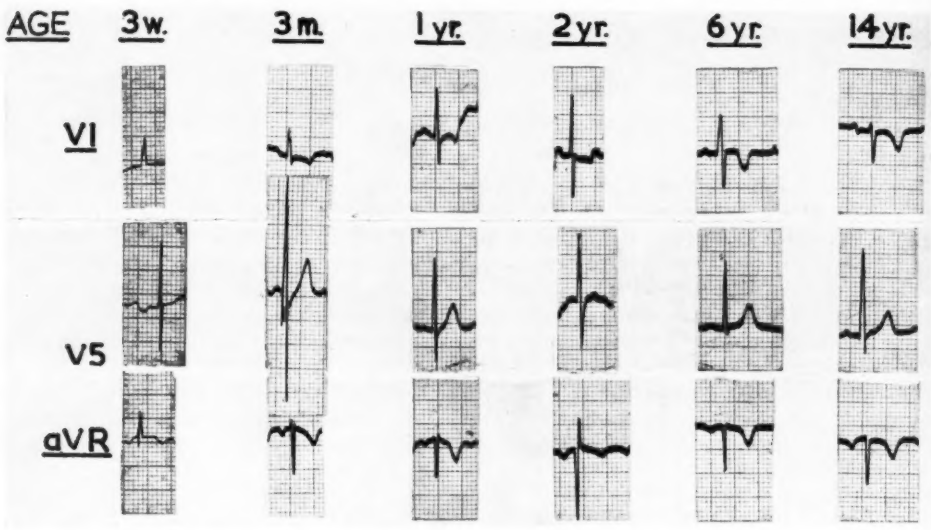


FIG. 1.—Representative normal electrocardiograms to show resolution of physiological right ventricular preponderance with age. Note that a dominant R in aVR does not occur over one month.

to 1·7 at one year and to 0·6 by five years: corresponding figures for V5 are 0·8, 2·9, and 7·8 (Gros *et al.*, 1951). It is therefore clear that specific numerical criteria must be used in order to distinguish a pathological from a physiological degree of R.V.H. at different ages.

Criteria were therefore formulated for use between the ages of one month and fifteen years, and these are presented in Table I. They were determined as follows. The various features of right ventricular hypertrophy were listed and then for each feature a numerical value was assigned which lay outside the normal value at a particular age. For example, the R/S ratio in lead V1 never exceeds 4·0 from four to eleven months of age, and it was therefore reasoned that when it equalled or exceeded 4·5 it could be taken as evidence of R.V.H. Similar reasoning was applied to all the other criteria. The normal values were obtained from several excellent publications on the cardiograms in normal children by various authors with a total experience of over 700 cases (Alimurung *et al.*, 1951; Gros *et al.*, 1951; Richman and Master, 1951; Schaffer *et al.*, 1950; Switzer and Besoain, 1950; Tudbury and Atkinson, 1950; Yu *et al.*, 1951; and Ziegler, 1951).

During the first five years of life there is a rapid change in the R/S ratio in leads V1 and V5 (Fig. 1) and this made it necessary to subdivide this age group closely in respect of these criteria.

Criteria were not determined for the first month of life since there is a rapid change in the cardiogram in this period. There would appear to be good evidence that the relative and actual amplitudes of the præcordial R and S waves are unaltered when right bundle-branch block is present (Barker and Valencia, 1949; Laham *et al.*, 1951; Myers *et al.*, 1948; and Kroop *et al.*, 1951) and cases with such block are therefore not excluded from being judged by these criteria, with the exception of the intrinsicoid deflection time in V1.

Criteria were worked out for the actual amplitudes (as opposed to the ratio) of the R and S waves in V1, V5, and aVR. They were not found to help in diagnosis and may in addition be misleading if the electrode placement is not precise since very high voltages may normally occur in V3 in normal children. For these reasons the use of these criteria is not recommended.

Material and Methods. Preserved hearts were available from 42 cases of congenital heart disease on whom cardiograms had been taken. A decision on the presence and degree of myocardial hypertrophy was made in each case by comparison with a normal preserved heart from a child of the same age. Twenty-nine of the hearts were found to have hypertrophy of the right ventricle only and these cases form the material of this report.

Age Groups. 1–3 months, 6 cases; 4–11 months, 13; 1–5 years, 6; 6–15 years, 4. Thus 19 cases (66%) were under the age of one year and therefore in an age group where the diagnosis of an abnormal degree of R.V.H. might be expected to be the most difficult. The most frequent anomalies were Fallot's tetralogy in 10 cases, transposition in 5, and total anomalous venous drainage in 3 cases.

TABLE I

CRITERIA FOR THE DIAGNOSIS OF RIGHT VENTRICULAR HYPERTROPHY FROM ONE MONTH TO FIFTEEN YEARS OF AGE

(1) Presence of a Q wave in V1.
(2) Onset of intrinsicoid deflection in V1 delayed to 0·04 sec. or more in the absence of right bundle-branch block.
(3) R/S or R/Q in aVR of over 1·0.
(4) P wave of 3 mm. or more in lead II, or 2·5 mm. or more in any other lead.
(5) Electrical axis of over +120°.
(6) R/S in V1 and V5 as below.

	1–3 months	4–11 months	1–2 years	3–5 years	6–15 years	
R/S V1	7·0	4·5	2·5	2·0	1·5	or more
R/S V5	0·5	0·7	0·8	0·9	0·9	or less

Analysis. The criteria for the diagnosis of R.V.H. as shown in Table I were applied to the findings in each case and the results tabulated and analysed. The cardiogram consisted of the standard and augmented unipolar limb leads and leads V1, V3, and V5 except for three cases in which the aV leads were not taken.

RESULTS

The frequency with which the various criteria were satisfied is shown in Table II. Of the 29 cases there were 25 (86%) in whom two or more criteria were present thus permitting a definite diagnosis of right ventricular hypertrophy to be made. Of the 4 remaining cases one criterion was satisfied in each of three cases and these are classed as having probable evidence of R.V.H. Details of these four are as follows. Case 9, aged 4 months, had tricuspid stenosis and pulmonary atresia with a normal thickness of compact myocardium but with very thick trabeculae in the right ventricle, and the R/S ratio in V5 was abnormally low. Case 5, aged 2 months, with Eisenmenger's complex, had a P wave in V3 of 3 mm. as the only abnormal feature. Case 20, aged 1 year, with Fallot's tetralogy had an abnormal electrical axis of +160°. The R/S ratio in V1 of 2·3 was close to the criterion value of 2·5. The fourth, Case 6, aged 3 months had complete transposition but no abnormal features apart from left axis deviation (axis −30°): this represents the only complete failure of diagnosis.

TABLE II

THE FREQUENCY WITH WHICH THE VARIOUS CRITERIA WERE SATISFIED IN A SERIES OF 29 CASES WITH RIGHT VENTRICULAR HYPERTROPHY CONFIRMED AT AUTOPSY

Age group	No. of cases	R/S ratio						
		V1	V5	aVR	Q in V1	P wave	Axis	Definite diagnosis in*
1–3 months	6	2	2	4	0	4	1	66%
4–11 months	13	11	7	8	5	8	3	93%
1–3 years	5	4	1	3/4	1	2	5	80%
4–15 years	5	5	3	2/3	3	2	3	100%
Total	29	76%	45%	66%	31%	55%	46%	86%

* i.e. two or more criteria satisfied.

DISCUSSION OF CRITERIA AND RESULTS

The evidence presented in the preceding section has shown that 86 per cent of a series of autopsy proven cases of right ventricular hypertrophy had *certain* evidence of such hypertrophy when using the criteria shown in Table I and that a further 10 per cent had *probable* evidence of R.V.H. Since these criteria were formulated on the basis of extensive studies on normal infants and children by various authors it is likely that they are reliable in differentiating pathological from physiological hypertrophy. Errors of diagnosis from their use may be in the direction of classing a case of R.V.H. as being normal—as with lead V1 of Case 20—rather than of making a false diagnosis of R.V.H. in a normal subject. This high incidence of correct diagnosis might be related to the fact that all the cases except two had considerable hypertrophy at autopsy, although a definite diagnosis was in fact made in these two cases also.

Influence of Age. As expected diagnosis was least successful in the age group one to three months where a certain diagnosis was made in only 4 of the 6 cases with a probable diagnosis in a further one. A curious finding, in contrast to the other age groups (see Table II), was the fact that the R/S ratio in leads V1 and V5 was abnormal in only a third and strictly normal in the remainder. In this age group the R/S in aVR and the P wave were the most commonly satisfied criteria.

The various criteria will now be considered individually.

R/S Ratio in V1. This criterion was satisfied more frequently than any other, being present in 76 per cent of cases. However in 7 per cent of normal infants aged one to three months Ziegler (1951) has found this ratio to have a value of infinity. The criterion should not therefore be used by itself as evidence of R.V.H. in this age group. The algebraic sum of R+S, as introduced by Alimurung *et al.* (1951), overcomes this difficulty and may prove more useful at this age.

R/S Ratio in V5. Although satisfied in only 45 per cent of the total, this lead has a particular value in the very young. As already mentioned the use of R/S V1 from one to three months is restricted by the fact that the normal and pathological ratios have a slight overlap. This objection does not apply to the ratio in V5 where figures far removed from the normal may be obtained. (Fig. 2 and 3).

Q Wave in V1. This was found in 31 per cent. It was never the sole abnormality in this lead and when it was present there were always abnormalities in other leads too. It thus appears to be a late sign of R.V.H. but does have the advantage of being an unequivocal abnormality at all ages.

Intrinsicoid Deflection in V1. This was delayed in 7 of the 20 cases (35%) without right bundle-branch block. All the cases had other evidence of R.V.H. in V1 and thus this criterion proved of no

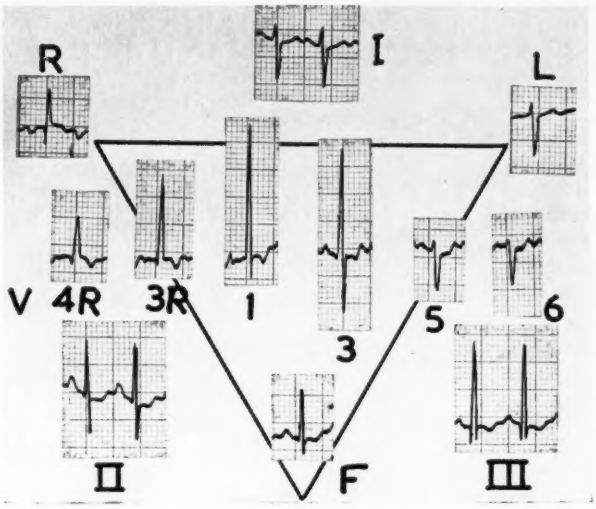


FIG. 2.—To show the particular value of lead V5 in the young infant. The R/S in V5 of 0·2 differs greatly, by over 300 per cent from the criterion value of 0·7, while in V1 the R/S ratio of 6·0 is only 30 per cent greater than the criterion of 4·5. Case of congenital mitral stenosis, aged 4 months with considerable R.V.H. (autopsy proof).

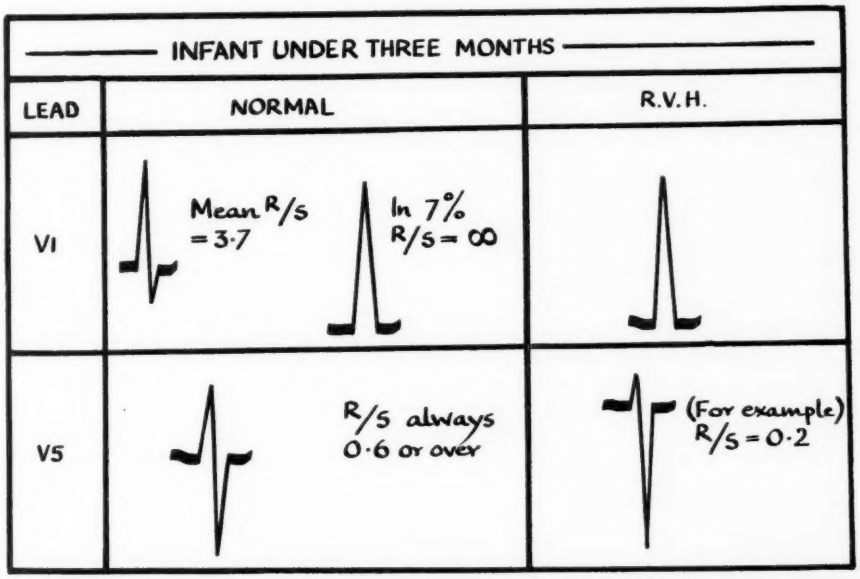


FIG. 3.—In infants under the age of 3 months the R/S ratio in V1 is normally quite high and in 7 per cent it reaches infinity. Thus, in contrast with adults, there is relatively little change from the normal to the abnormal pattern. In lead V5 however there is ample scope for change to an abnormal pattern.

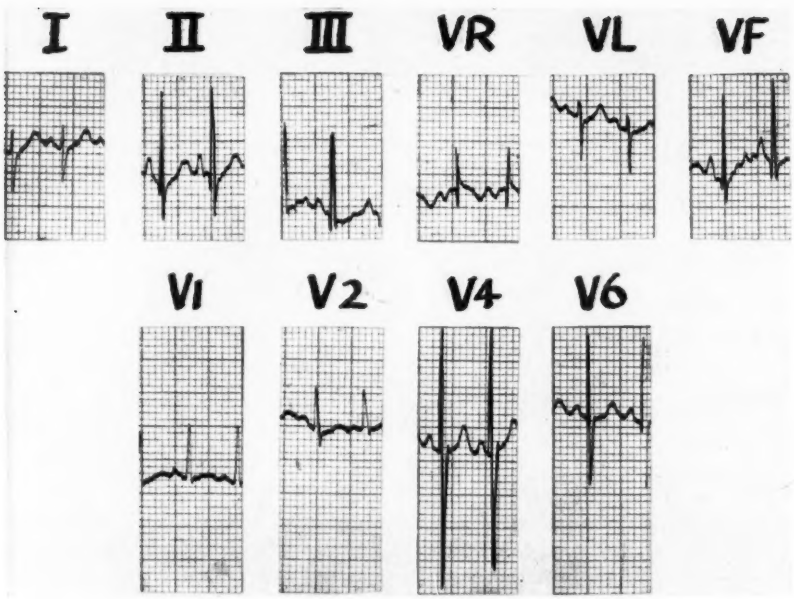


FIG. 4.—The R/S ratio in V1 of 8·0 (*criterion* 7·0), and in aVR of 2·0 (*criterion*, over 1·0) together with the 3 mm. P wave indicate a pathological degree of right ventricular preponderance. Case of atrial septal defect, aged 2 months, with moderate R.V.H. (autopsy proof).

help in diagnosis. The incidence is lower than that of 53 per cent given by Sokolow and Lyon (1949) who found it to be the most commonly encountered criterion of R.V.H.

Slurring or notching of a tall R wave in V1, usually near its base, is a fairly common finding in cases of congenital heart disease with R.V.H. In such cases a diagnosis of bundle-branch block would seem to be misleading since the main change present is that of ventricular hypertrophy. The vectorcardiographic work of Lasser and Grishman (1951) supports this view.

Lead aVR. R/Q or R/S ratios exceeding 1·0 were found in 17 cases (65%) and denoted an abnormality in 5 in which the actual amplitude of the R wave was normal. Lead aVR was abnormal in two cases where lead V1 was normal in all respects and this combination has been reported too by Goodwin (1952) and by Myers *et al.* (1948).

Lead aVF. The R wave was the major QRS component in 76 per cent of cases but it exceeded the normal maximum of 20 mm. in only one.

Electrical Axis. An abnormal degree of right axis deviation was found in 16 cases (55%) and in one it was the sole abnormality. In 5 cases the axis was negative, ranging from −30° to −127°, two of these being very unusual in that it lay between −90° and −180°. The occurrence of left axis deviation in R.V.H. has been particularly studied by Kroop *et al.* (1951) and by Lasser and Grishman (1951), who found that the determining factor was a tall R wave in aVL greater than the R in aVF: this was found to be so in 4 of the 5 present cases.

Electrical Position. According to criteria of Wilson *et al.* (1944) the electrical position of the heart was horizontal in 16 (61%), semi-horizontal in three, intermediate in one, vertical in one, and indeterminate in four. As Woods (1952) suggested, the electrical position as determined by Wilson's criteria are more in accord with the anatomical position of the heart than when determined by the criteria of Goldberger (1949).

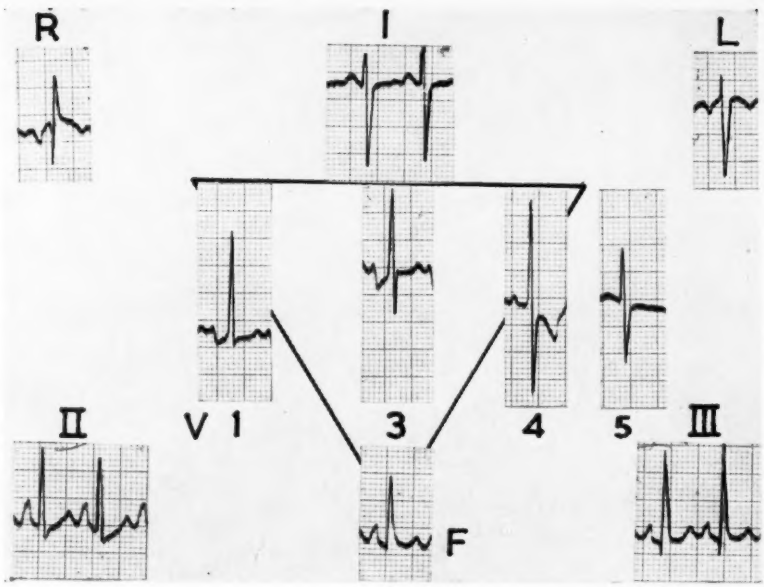


FIG. 5.—The R/S ratios in V1 of 19 (*criterion* 2·5) and in V5 of 0·8 (*criterion* 0·8) indicate right ventricular hypertrophy as does the P wave of 4 mm. (*criterion* 3 mm.). Case of mitral atresia and ventricular septal defect, aged 1 year, with considerable R.V.H. (autopsy proof).

P wave. Abnormally tall P waves were found in one or more leads in 17 cases (57%), most frequently in leads II, aVF, and V3. The mean duration of the abnormal P waves of 0·06 sec. is normal.

SUMMARY

The usual adult criteria for right ventricular hypertrophy are inapplicable in infants and young children because of the presence of physiological R.V.H. Special numerical criteria have therefore been constructed for various age groups from one month to fifteen years. Their reliability has been established by applying them to an autopsy series of lone right ventricular hypertrophy. It was found possible to differentiate pathological from physiological hypertrophy in 86 per cent of this series and to make a probable differentiation in a further 10 per cent.

The most common finding was an abnormally high R/S ratio in V1. Under three months of age the normal and abnormal figures for this ratio have a slight overlap that may make diagnosis uncertain from this lead alone. However there is ample scope for change to a grossly abnormal pattern in V5 which thus has a particular value in the very young.

It is a pleasure to thank Dr. Arnold L. Johnson for kindly providing the facilities for this work and for his helpful suggestions and criticism. Dr. F. R. Wigglesworth and Dr. R. de Pape provided the pathological data and their help is gratefully acknowledged.

REFERENCES

Alimurung, M. M., Joseph L. G., Nadas, A. S., and Massell, B. F. (1951). *Circulation*, **4**, 420.
Barker, J. M., and Valencia, F. (1949). *Amer. Heart J.*, **38**, 376.
Cabrera, E. and Monroy, J. R. (1956). *Amer. Heart J.*, **43**, 667.

Goldberger, E. (1949). *Unipolar Lead Electrocardiography*. 2nd. ed., H. Kimpton, London.
Goodwin, J. F. (1952). *Brit. Heart J.*, **14**, 193.
Gordon, A., and Goldberg, H. (1951). *Amer. Heart J.*, **41**, 226.
Gros, G., Gordon, A., and Miller, R. (1951). *Pediatrics*, **8**, 349.
Kroop, I. G., Steinberg, M. F., and Grishman, A. (1951). *Amer. Heart J.*, **41**, 891.
Laham, J., Gialloreto, O., and Lenegre, J. (1951). *Acta Cardiol. Brux.*, **6**, 129.
Lasser, R. P., and Grishman, A. (1951). *Amer. Heart J.*, **41**, 901.
Myers, G. B., Klein, H. A., and Stonfer, B. E. (1948). *Amer. Heart J.*, **35**, 1.
Richman, B., and Master, A. M. (1951). *Amer. Heart J.*, **41**, 687.
Schaffer, A. I. (1950). *Amer. J. Dis. Child.*, **80**, 260.
——, Burstein, J., Mascia, A. V., Barenberg, P. L., and Stillman, N. S. (1950). *Amer. Heart J.*, **39**, 588.
Sokolow, M., and Lyon, T. P. (1949). *Amer. Heart J.*, **38**, 273.
——, and Edgar, A. L. (1950). *Amer. Heart J.*, **40**, 232.
Switzer, J. L., and Besoain, M. (1950). *Amer. J. Dis. Child.*, **79**, 449.
Tudbury, P. B., and Atkinson, D. W. (1950). *J. Pediat.*, **36**, 466.
Veasey, L. G., and Adams, F. H. (1952). *Pediatrics*, **9**, 395.
Wilson, F. N., Johnson, F. D., Rosenbaum, F. F., Erlanger, H., Kossmann, C. E., Hecht, H., Cotrim, N., Memezes de Olivera, R., Scarsi, D., and Barker, P. S. (1944). *Amer. Heart J.*, **27**, 19.
Woods, A. (1952). *Brit. Heart J.*, **14**, 193.
Yu, P. N. G., Joos, H. A., and Katsampes, C. P. (1951). *Amer. Heart J.*, **41**, 91.
Ziegler, R. F. (1951). *Electrocardiographic Studies in Normal Infants and Children*. Springfield, Charles C. Thomas.
——, (1956). *Amer. Heart J.*, **52**, 533.

THE NATIONAL HEART HOSPITAL
1857–1957

A hundred years have passed since the National Hospital for Diseases of the Heart, to use its older title, was founded by Dr. Eldridge Spratt, and for some years he was the only Physician and often Treasurer and Secretary as well. The first eighteen years were more like a Victorian melodrama than a history of a Victorian hospital. On many occasions, almost from the time a Committee was first appointed—and there were many of them for few members stayed long—there was trouble between the Committee and Dr. Spratt. At one meeting attended only by Admiral Burney (Chairman, 1869–1874) and Dr. Spratt, a resolution was passed and recorded that "the entire management should be under Dr. Spratt."

Mention should be made of Captain Dodson, late Royal Marines, who became Secretary in 1868 for he advanced money from his own pocket and collected enough to pay off many of the old debts of the Hospital—some for the original equipment bought in 1857. And in 1872 he found a Treasurer, his friend the Earl of Glasgow, who was Chairman from 1875 to 1881 when the Hospital was really finding its feet.

In 1874, a fine house in a corner of Soho Square was found and became the home of the Hospital for forty years. It had been the home of the Linnean Society and had been built by the Adam brothers for Sir Joseph Banks, who was President of the Royal Society from 1778–1820 and a great botanical collector and one of the founders of Kew Gardens. He travelled to Australia with Captain Cook in the *Endeavour* (1768–71) and Botany Bay was so named because of the many botanical specimens he collected when he landed there. His life has been recorded by H. C. Cameron in *Sir Joseph Banks, K.B.* (1952 : The Blatchworth Press, London).

But the difficulties had not yet been overcome. These became so acute that after some financial irregularities Dr. Spratt, the founder, was asked by the Committee to resign. He refused but the Committee was now made of sterner stuff, and in 1875 a meeting presided over by Colonel Robertson-Aikman, V.C. (Vice-Chairman at the time, and Chairman, 1881–1890) removed his name from the list of Physicians. The Committee left the Hospital, but Dr. Spratt in the middle of the night returned with a furniture van and removed many of the contents of the Hospital.

1875–1914. Gradually under the guidance of the Earl of Glasgow (1875–1881) and his successor Colonel Robertson-Aikman (1881–1890) the finances of the Hospital were put on a firmer basis and the medical staff were able to carry on their work without interruption. Out-patient sessions were held regularly and the physicians, now four in number, saw an increasing number of out-patients with heart disease and did all they could for them. Perhaps the treatment was not very different from that obtained elsewhere and no great discoveries seem to have been recorded by the medical staff. Their publications, recorded in the medical directories of the time, show that they did not confine their interests to heart disease, for they include *Hints on Men and Women* by Dr. Ambler (1875), *The Effect of Education on the Industrial Classes* by Dr. Duncan (1878), and *Cycling as a Cause of Heart Disease* by Dr. Herschell (1893).

Dr. R. O. Moon (1902–30), a classical scholar and a medical historian, was the first Physician of the hospital to be elected a Fellow of the Royal College of Physicians, though Dr. Aldis who was appointed a Consulting Physician in 1872 had been a F.R.C.P. since 1838. Moon thought that the advance to a more modern approach was first made by Dr. Charles W. Chapman (1893–1914), who died at the age of ninety-seven, as late as 1940. Chapman wrote a book, *Heart Disease in Childhood and Youth* (Medical Publishing Company, London, 1900), and the introduction by

Sir Samuel Wilks also emphasizes that he had " arrived at more favourable conclusions than have generally been suspected."

The last years of the Hospital at Soho Square were, however, marked by great progress, for under the stimulus of Dr.—later Sir Sydney—Russell-Wells (1905–1924), M.P., and later Vice-Chancellor of London University, a pathological department was opened in an iron shed in 1910, and an X-ray department in another shed. The first electrocardiograph had a curious history for it was purchased in 1911—a half share by the Hospital and a half share by the famous Professor A. D. Waller, whose researches from 1887 onwards recording the electrical activity of the heart with a capillary electromanometer laid the foundations on which modern electrocardiography has been built. As there was no room at the Hospital, it was housed in his physiological laboratory at South Kensington, and the patients were taken there by cab. During this partnership which lasted for two years, Dr. Waller, F.R.S., became Consulting Physician to the Hospital, joining Sir Frederick Taylor (P.R.C.P., 1915–1918) who had been appointed in 1910.

In 1912 plans were made for a new hospital in Westmoreland Street. Sir James Harrison, K.C.V.O. (Chairman, 1913–1921), Sir Sydney Russell-Wells, and Captain Whitney, who had just become Secretary of the Hospital—and still is—deserve the main credit for this. The new buildings were opened in 1914—a striking commentary on what could be done with energy and initiative in those days by the voluntary hospitals, even by a small hospital with no endowments. Since then progress has been uninterrupted.

1914–1957. Almost at once the war intervened. The Hospital became one of the main centres for examination of the hearts of recruits who were referred by army medical boards. Ten thousand were examined and some conclusions were published by the medical staff in 1918 (*Brit. med. J.*, **1**, 556 and **2**, 248). Sir Sydney Russell-Wells in address on *The Aim and Use of Special Hospitals* (*J. Laryng.*, 1923, **38**, 173) showed his foresight by urging many develoments of postgraduate teaching that have since taken place, though unfortunately, we have not reached his vision of a quiet square with the different special hospitals and a residential college for the postgraduate students built round it. He thought that under-graduates should be taught in the special departments of general hospitals, but that the special hospitals were ideal for postgraduate teaching, and that they should be federated to constitute a London Postgraduate School.

Dr. Frederick Price (1914–1937), known throughout the world for the *Textbook of Medicine* he edited, and Dr. Strickland Goodall (1914–1934), a popular teacher, showed by the large consulting practices they developed that the public wished to benefit from the growth of cardiology as a branch of Medicine. The reputation of the Hospital was widened by the work that was done under the leadership of Sir John Parkinson (1920–1950) in association with the late Dr. Parsons-Smith (1920–1947) as Dean and Dr. Thomas Cotton (1924–1949).

Regular out-patient teaching and special courses were started in 1919, although some post-graduate teaching had been discussed by the Committee as early as 1874. The Hospital has always been a small one and much of its reputation was built on the teaching at the large out-patient clinics, where electrocardiograms and X-rays were available, a form of teaching that could then cover most aspects of cardiology. Nevertheless, the work for in-patients was important and the Hospital was fortunate in having many distinguished resident medical officers: those from overseas included H. L. Heimann of Johannesburg (1922), E. F. Gartrell of Adelaide (1925), G. A. Elliott of Cape Town and Johannesburg (1932), and Clive Fitts of Melbourne (1933); and those from this country, Robert Marshall (1914)—the first in Westmoreland Street—C. W. Curtis Bain (1923), K. Shirley Smith (1927), P. H. O'Donovan (1928), J. R. H. Towers (1931), Paul Wood (1934), Evan Jones (1935), E. P. Sharpey-Schafer (1936), and Graham Hayward (1936).

The annual St. Cyres Lecture has been the most important outside occasion of the Hospital. It has been delivered by many men famous in cardiology, including K. F. Wenckebach (1928), John Cowan (1930), Thomas Lewis (1931), John Hay (1933), Paul White (1935), Charles Laubry (1937), Samuel Levine (1948) Pierre Duchosa (1951) and Lewis Dexter (1955).

Registrars were appointed for the first time in 1946, though Clinical Assistants had been

working in the Out-patient Department for a long time. In 1948 a real Pathological Department was made in the mews at the back of the Hospital—spacious compared with its old quarters for a part-time pathologist, but sadly cramped for the valuable work it now does under the direction of Dr. Reginald Hudson.

With the coming of the National Health Service in July, 1948, the Hospital became a Post-graduate Teaching Hospital with its own Board of Governors. The Medical School, which has been growing since 1919, was reborn as the Institute of Cardiology. This was established in 1947 under the auspices of the British Postgraduate Medical Federation in the University of London, and owes much to Sir Francis Fraser and to its first Chairman, Lord Brabazon of Tara, now succeeded by Mr Michael Perrin. It has led to a much fuller teaching programme for whole-time students as well as the shorter special courses. Equally important, it has acquired some new premises so that there is more room for laboratories, and the physicians and registrars have been able to widen the range of their research work from the purely clinical.

For some years the policy of the Governors of the Hospital has been to assemble on the medical staff physicians from various teaching London hospitals who have shown by research and teaching their special interest in circulatory diseases. Thus all the physicians on the present staff are physicians of other teaching hospitals in London—Maurice Campbell (Chairman of the Medical Committee), Evan Bedford, Paul Wood, William Evans, Graham Hayward, and Wallace Brigden, and last but not least as cardiac surgeon, T. Holmes Sellors, who will have facilities for his surgical work in the hospital that is to be rebuilt in the near future. This has led to a friendly exchange of ideas and has been a powerful factor in making the Hospital and the Institute a national centre for research and postgraduate teaching in cardiology.

There is no reason to think that Dr. Eldridge Spratt was an outstanding physician. Certainly he was quarrelsome, egotistical, resentful of control, and financially irresponsible if not worse. But we cannot forget that at a time when little interest was taken in diseases of the heart, most of which were thought to have a grave significance and to be incurable, he had the foresight and driving energy to found a hospital for their study, the first in the world devoted solely to the study and treatment of the heart.

MAURICE CAMPBELL

I am indebted to Captain Whitney (Secretary, since 1912) for the notes about the early history and for most of the dates. The first annual report that is extant is that of 1864 and since 1871 most have been preserved. Captain Whitney has been through these and the old minute books and has recorded the history of the Hospital in two small books that have been privately printed—*The Place of Hearts*, 1857–1937 and 1938–1957.

To celebrate the Centenary of the Hospital, a dinner was held in the Hall of the Society of Apothecaries, by kind permission of the Master and Court, on Wednesday, October 2, to which many distinguished guests were invited. On Thursday, October 3, the Medical Staff of the Hospital and of the Institute of Cardiology invited a small number of guests to take part in a symposium on some aspects of congenital heart disease. An account of this will be published in the next number of the British Heart Journal.

CASE REPORTS

ACONITINE-INDUCED CARDIAC ARRHYTHMIA

BY

GEOFFREY FFRENCH

From the Queensway General Hospital, and the Oakville-Trafalgar Memorial Hospital, Toronto

Renewed interest in the pharmacological action of aconitine has followed the work of Sherf (1947), Prinzmetal *et al.* (1950 and 1951), and Brown and Acheson (1952).

Its use in experimental medicine produces stimulus formation in the dog's heart with auricular tachycardia and in certain circumstances ventricular tachycardia and fibrillation: it has become a useful tool in the hands of the research cardiologist. On the other hand though it has long been used by physicians both externally and internally, there is very little information as to its effect upon the human heart and circulation. Such as there is has been confined to the observation of the pulse rate and character. Hartung (1930) described electrocardiographic changes in a case of aconite poisoning which demonstrated a sinus bradycardia and first degree heart block; since then no further evidence has been published and it is the purpose of this communication to report a case with unequivocal evidence of the relation of the drug to the arrhythmia. Before doing so, some facts about this interesting alkaloid may be useful.

Materia Medica

Aconitine and its allied alkaloids (aconine and benzaconine) are the active principles of *Aconitum napellus* whose synonyms, Monkshood, Wolfsbane, Jacob's chariot, etc., are well known and comprise a number of sub-species; it is a perennial tuberous root growing wild in the mountainous districts of Europe and Asia, the commercial supplies coming from Western Europe.

In modern times aconite has been used principally for its dual effects; it has a peripheral action in stimulating sensory nerve endings in the skin and mucous membranes and has been used for many years as a counter-irritant: there is still a preparation in the British Pharmacopœia, Linimentum Aconitum but the danger of its systemic effects has led to its gradual disuse. These effects, mainly stimulation of the medullary vagal centres with slowing of the heart and lowering of the blood pressure were also utilized in the treatment of fevers, usually in the form of tincture of aconite. The masterly accounts in Taylor's Jurisprudence (Smith, 1948) of deaths by suicide and homicide in the 19th century when the drug achieved some popularity, are unique.

The classical symptoms of aconite absorption and intoxication are shared only to a much less degree by veratrine. Tingling and numbness of the tongue occur shortly after ingestion and these symptoms persist and extend to involve the whole body, accompanied by acute restlessness, vomiting, shock, muscle twitchings, and convulsions; many of the reported cases have exhibited trismus. Veratrine has only a slight tingling effect which does not persist. The pulse is at first slow but later becomes rapid and irregular; the blood pressure falls and death occurs from respiratory paralysis and ventricular fibrillation. The persistent numbness and tingling is apparently characteristic of aconite intoxication and its recognition is therefore of cardinal importance.

The minimum lethal dose has been as low as 1/50 of a grain (1·2 milligrams) of the pure alkaloid aconitine (Smith, 1948) but when considering toxic doses the admixture of allied alkaloids must be kept in mind, and their presence has often been confusing to the analyst. When recovery occurs, the effects of intoxication may persist for several weeks, with great muscular weakness, paræsthesiae, numbness, tingling, and formication. By reason of its vagal inhibiting effect, the most useful antidote is atropine, but all methods must be used to combat shock including circulatory stimulants and oxygen. It can be neutralized in the stomach by tannic acid followed by charcoal (Martindale, 1952).

Case Report

A laboratory technician, aged 32, consumed on 17/12/55 200 mille-litres of an infusion of what he thought was *Echinacea angustifolians*, after his wife, to whom he had offered it, had refused to

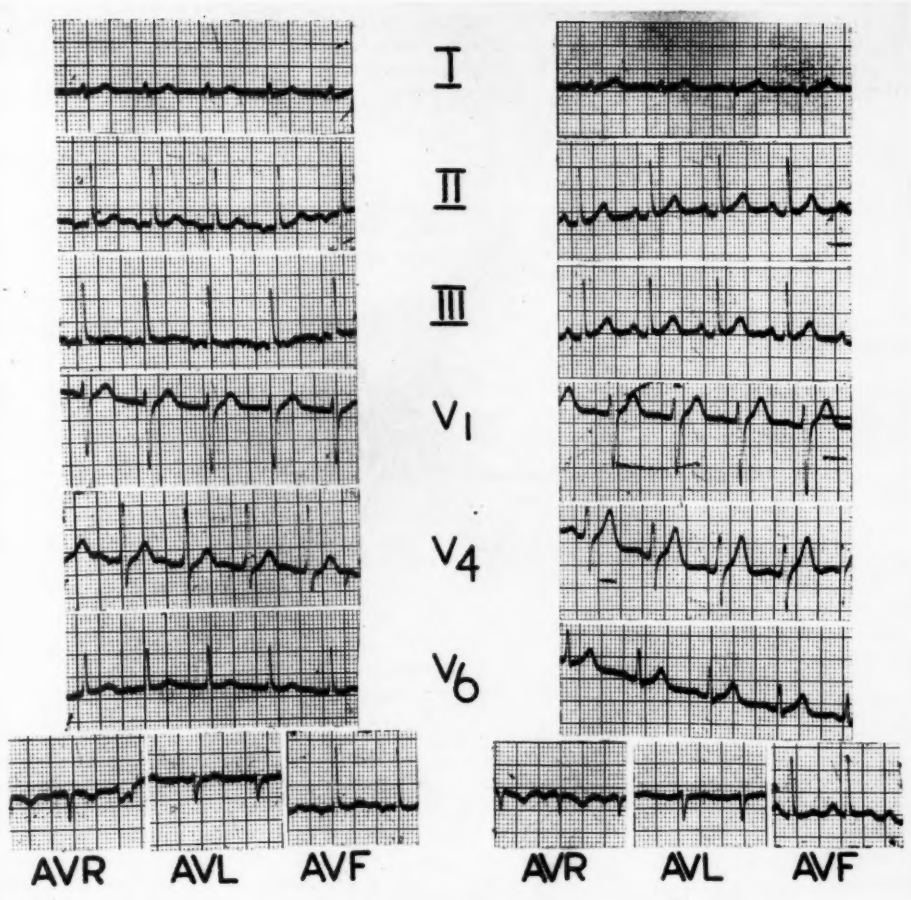


FIG. 1.—(A) Electrocardiogram of 18/12/55, showing auricular tachycardia at 115 a minute. (B) Electrocardiogram of 22/12/55, showing return of sinus rhythm at 100 a minute.

drink any more because it made her tongue numb. She had had symptoms of lower abdominal pain earlier in the day and her husband had made the infusion originally for her relief. He had been in the habit of drinking similar infusions for the past few years, mainly as a tonic to " thicken the blood." Two and a half hours later he began to have difficulty in getting his breath and rapidly became cyanosed and shocked, with a rapid faint pulse and a systolic blood pressure of 60 mm. Hg. He was removed at once to hospital where he was given warmth and oxygen. By this time he was complaining of abdominal cramps and was vomiting repeatedly. He said his whole tongue and body felt numb and tingling and he complained increasingly of this together with great muscular weakness. In view of his history of taking a herbal infusion and the numbness complained of both by his wife and himself, the possibility of aconitine or veratrine poisoning was considered, these being the only drugs known to have such an effect. Atropine, 1/60 of a grain (1 mg.) was given intravenously and methedrine 15 mg. intravenously and 15 mg. intramuscularly, after which the blood pressure rose to 80/60 with temporary relief of cramps and weakness; these symptoms returned

after half an hour when the blood pressure had again fallen to 60 mm. Hg. A further 30 mg. of methedrine was given intramuscularly and from then on the state of shock gradually lessened; the vomiting decreased and it was possible to achieve gastric lavage with sodium bicarbonate and leave activated charcoal in the stomach. The pulse all this time was extremely fast, even prior to the atropine. He was sent to the ward with a blood pressure of 100/60 still complaining of numbness of tongue and body: his speech was thick as if his tongue was too big, and he had great muscular weakness with absent reflexes but no other abnormal signs.

He had recurrent bouts of abdominal cramp and vomiting during the night but his general condition gradually improved and by the following morning his blood pressure was 110/70. He still had tachycardia and the electrocardiogram showed an auricular tachycardia of 115 a minute (Fig. 1). He remained in hospital four days, with gradual lessening of all symptoms and was discharged apparently fully recovered although his pulse was still 100 a minute. A repeat electrocardiogram on the next day showed a return to normal rhythm with a sinus tachycardia of 100. Over the next few days the heart settled to between 70 and 80; his subsequent progress has been excellent and he returned to work one week after discharge from hospital and has remained well to date (October, 1956).

Pharmacological Identification and Assay. By Dr. R. M. Baxter, Ph.D., Faculty of Pharmacy, University of Toronto. The sample of drug was identified as containing aconite root and assayed 0·44 per cent of total alkaloids calculated as aconitine. The alkaloid aconitine was isolated and identified: the melting point was 194° centigrade with decomposition. The fluid taken by the patient, when assayed, revealed that it contained 22 mg. per 100 ml. (0·022%) of alkaloids. The patient was thought to have consumed 200 ml. of the infusion, that is 44 mg. of total alkaloids.

This patient was known to be in the habit of taking herbal infusions when unwell. After information from the family doctor that the patient was acutely ill, inquiries were made as to whether he had taken any herbs; and on this being confirmed aconite poisoning was suspected and the measures taken early in his illness probably contributed to his recovery. There is little more to be said except that this case re-emphasizes the possible danger of herbal medicines prepared from unknown sources.

Summary

A report is made of a case of aconite poisoning with recovery. Electrocardiographic studies revealed an interesting arrhythmia which reverted to normal. A brief review of the drug is given.

My thanks are due to Dr. Zaborowska, the patient's medical attendant, and to Dr. R. M. Baxter and Dr. George Walker, of the Faculty of Pharmacy, University of Toronto.

References

Brown, B., and Acheson, G. (1952). *Circulation*, **6**, 529.
Hartung, E. F. (1930). *J. Amer. med. Ass.*, **95**, 1265.
Martindale. (1952). *Extra Pharmacopœia*. 23rd ed., vol. 1, London.
Prinzmetal, M., Corday, E., Brill, I. C., Sellers, A. L., Oblath, R. W., Flieg, W. A., and Kruger, H. E., (1950). *Circulation*, **1**, 241.
——, ——, Oblath, R. W., Kruger, H. E., Brill, I. C., Fields, J., Kemamér, S. R., Osborne, J. A., Smith, L. Allen, Sellers, A.L., Flieg, W., and Finston, E. (1951) *Amer. J. Med.*, **11**, 410.
Scherf, D. (1947). *Proc. Soc. Exp. Biol. and Med.*, **64**, 233.
Smith, Sydney (1948). *Taylor's Principles and Practice of Medical Jurisprudence*. 10th ed., p. 636. London.

SUPRA-AORTIC STENOSIS ASSOCIATED WITH MARFAN'S SYNDROME

BY

A. F. BURRY

From the Department of Pathology, Christchurch Hospital, New Zealand

The association of arachnodactyly with other skeletal abnormalities and with ocular and cardiac malformations is now well recognized, and numbers of cases illustrating the syndrome have been reported in recent years. The main cardiac malformations have been degeneration of the aortic media with dissecting aneurysm or aneurysmal dilatation, usually of the ascending aorta, but coarctation, changes in the pulmonary artery, atrial septal defect, and valvular lesions have also been described. The mitral valve is said to be affected more frequently but the aortic valve also may show thickening of the cusps. Aortic regurgitation is common, due to dilatation of the ring rather than to the valvular lesions. The following case is of interest in that Marfan's syndrome was accompanied by aortic *stenosis* of a type apparently not previously reported.

Case Report

A woman, aged 37, congenitally mentally defective, was first admitted to the Christchurch Hospital at the end of August, 1955, with signs of congestive heart failure of some three weeks' duration. She showed some features of Marfan's syndrome. She had long slender limbs, the characteristic facies, a high arched palate, a moderate kyphoscoliosis, and a myopic stare. She had a rapid thready pulse. The blood pressure was 150/125, and later 130/110. The apex beat was in the seventh intercostal space at the mid-axillary line and there was other clinical evidence of gross left ventricular hypertrophy with also a suggestion of right ventricular enlargement. There was a triple rhythm on auscultation but no significant murmurs were detected. The neck veins were congested to the angle of the jaw, and there was sacral and ankle œdema. Moist sounds were heard at both lung bases and the liver was enlarged four fingers below the costal margin. A chest X-ray confirmed a gross enlargement of the transverse diameter of the heart and showed evidence of moderate pulmonary vascular congestion. An electrocardiogram was interpreted as showing P-pulmonale, a vertical heart in clockwise rotation, sinus rhythm at 160 a minute, and ventricular extrasystoles. A blood count was normal and other investigations were normal.

The family history was unrevealing and no evidence of stigmata of Marfan's syndrome in other members of the family could be elicited on subsequent inquiry. Previous ophthalmological examination had shown a moderate myopia but no dislocation of the lenses of the eyes.

The cause of the cardiac enlargement remained in doubt. There were features against hypertension and aortic stenosis, the likely diagnoses, and a history of rheumatic fever was lacking. The patient's condition was improved considerably by full digitalization and she was discharged a month after admission without a firm diagnosis.

A week later she was readmitted to hospital gravely ill. She had been well until the morning of admission when she awoke complaining that her feet felt dead. She then complained of severe abdominal pain which wore off a little and then returned to spread and involve arms, legs, and chest. She became acutely dyspnœic with laboured bubbly respirations. On admission she was very cyanosed, sitting upright and struggling for breath. The extremities were cold and the pulse at the wrist was rapid and almost imperceptible. The blood pressure was 130/110. There was only slight sacral and ankle œdema but the jugular venous pressure was raised and the liver still enlarged. The femoral pulses were absent, and both legs were cold and blue. Râles were widespread in both lungs. The abdomen was rigid, distended, and tympanitic, and bowel sounds were absent. Towards evening the patient started to vomit small amounts of brownish fluid. The respirations were bubbly and cyanosis persisted. She died 15 hours after the onset of pain.

Necropsy. The body was that of a small middle-aged woman in a fair state of nutrition. The left pleural cavity contained 500 ml. of clear straw-coloured fluid and there were traces of fluid in the right pleural cavity and pericardial sac. The abdominal cavity contained watery blood-stained fluid.

The *heart* weighed 540 g. and showed gross left ventricular hypertrophy. The left atrium was dilated. The left ventricular wall was thinned towards the apex where there was slight fibrosis of the myocardium and fibrosis of the endocardium to which masses of soft friable thrombus were adherent. There were small thrombi also in the right auricular appendage. The mitral, pulmonary, and tricuspid valves were normal. The coronary arteries showed atherosclerosis with many constrictions but no major occlusions.

The main interest of this case lies in the *aorta* which was grossly constricted at its origin by two valvular ridges *above* the aortic valves (which were present and normally formed). Viewed from above (Fig. 1) there

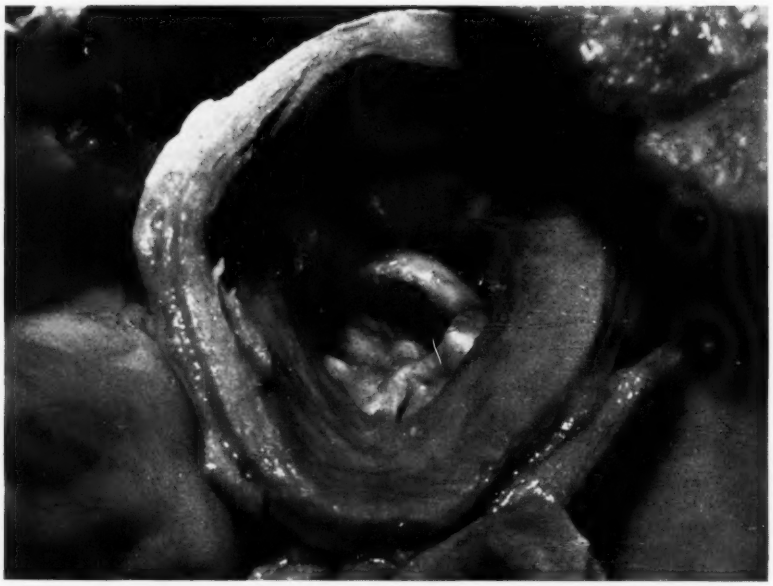


FIG. 1.—Abnormal valves viewed from above. Note marked constriction of aorta at valvular opening.

is seen to be a progressive expansion of the aorta from the point of constriction although at full calibre it appeared a little smaller than normal. The aortic wall was slightly thickened. The abnormal valves extended around the aorta immediately above the aortic valve commissures (Fig. 2) which fused with them. The aortic valves were of normal size but slightly thickened, and their margins were apposed by the constriction with consequent deepening of the sinuses of Valsalva, which formed deep pouches. In the depths of the sinuses the coronary arteries arose normally.

Microscopic Findings. Sections showed the abnormal valves to be composed of fibro-muscular tissue with rather scanty elastic fibres. Towards the free border there was hyaline collagenous tissue which included a small area of calcification. Applied to both upper and lower surfaces of the ridge were cushions of fibrous tissue thickening the intima and apparently derived from organization of thrombus. Sections of the aorta above the constriction showed slight thickening when compared with controls of similar age. The inner half of the media was deficient in elastic fibres and composed of rather loose fibromuscular tissue. No actual degenerative changes or medio-necrosis could be demonstrated.

Sections from the apex of the left ventricle showed the fibrosis to be mainly an endocardial thickening consisting of laminated fibrous tissue which merged with organizing thrombus of varying age. Deeply the myocardium was thinned with atrophy of many muscle fibres and replacement by hyaline fibrous tissue.

Other Findings. The aorta contained a number of large emboli and smaller emboli were demonstrated occluding the superior mesenteric artery from just beyond its origin, the splenic and hepatic arteries, and both external iliac arteries. The lungs showed an early pneumonic reaction to inhaled vomitus. The stomach and upper small intestine were distended with fæculent fluid. The remainder of the jejuno-ileum was dark and necrotic from early infarction. The liver showed chronic venous congestion. The brain showed no striking abnormality macroscopically.

Post-mortem Diagnosis. Congenital supra-aortic stenosis. Endocardial thrombosis? on small infarct. Multiple embolism with infarction of small intestine. Inhalation of vomitus.

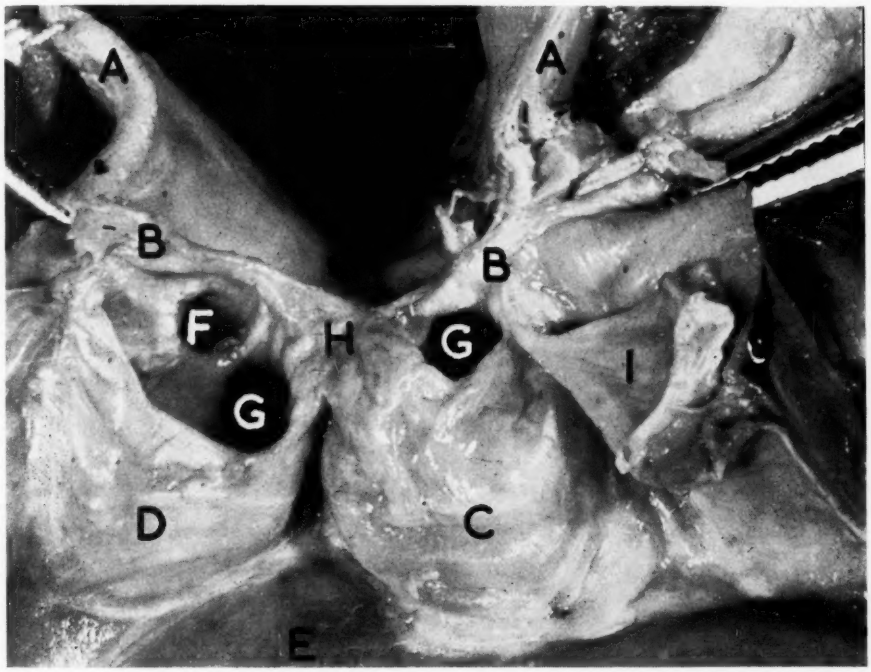


FIG. 2.—Opened specimen, showing from above down: (A) aortic wall; (B) abnormal ridges; (C) anterior and (D) left posterior aortic valve cusps; (E) upper left ventricular wall. On the left (F) the opening of the left coronary artery is well seen. Note deepening of sinuses of Valsalva (G), and slight fusion of commissures which merge with the abnormal ridges at (H). The right posterior aortic valve cusp (I) has been divided and partly removed.

Comment

Probable Sequence of Events. The gross stenosis of the aorta resulted in severe left ventricular hypertrophy. Heart failure may have been precipitated by a small infarct at the apex of the left ventricle although the area of muscle necrosis was very slight. The degree of endocardial fibrosis would suggest that organizing thrombus had been present for considerably longer than the two months which was the total duration of symptoms. The endocardial thrombosis may be the result of aortic stenosis alone and the myocardial fibrosis a secondary change. When a fragment of thrombus became dislodged it is possible that it became wedged in the constricted ventricular outlet initiating severe circulatory failure. Its sudden passage through the opening would cause a change in intraventricular pressure and would tend to dislodge further masses of thrombus.

Nature of the Malformation. The essential abnormality appears to be an infolding of the inner

aortic wall immediately above the aortic valve, with formation of two valvular ridges. It is difficult to postulate any origin for these appearances other than a congenital malformation. There is no evidence of rheumatic or other inflammatory process in the aortic valves proper. There is some resemblance to coarctation but, while coarctation distal to the usual site has been described, I can find no record of any proximal to the origin of the great vessels. The changes in the aortic media fall short of those classically associated with Marfan's syndrome but other clinical features justify the diagnosis. It seems likely that the aortic malformation is related to these changes in the media.

Summary

A case of Marfan's syndrome with a new aortic malformation is described. This abnormality consisted of a gross constriction of the aorta immediately above the aortic valve, with formation of two valvular ridges.

For permission to publish this case I have to thank Dr. F. O. Bennett under whose care the patient was admitted, and Dr. T. Morton, Medical Superintendent. I also wish to thank Dr. D. T. Stewart for help and advice in preparing this report.

TRACHEAL VASCULAR RING CAUSING DYSPNŒA

BY

N. COULSHED AND E. WYN JONES

From the Liverpool Regional Cardiac Centre, Sefton General Hospital

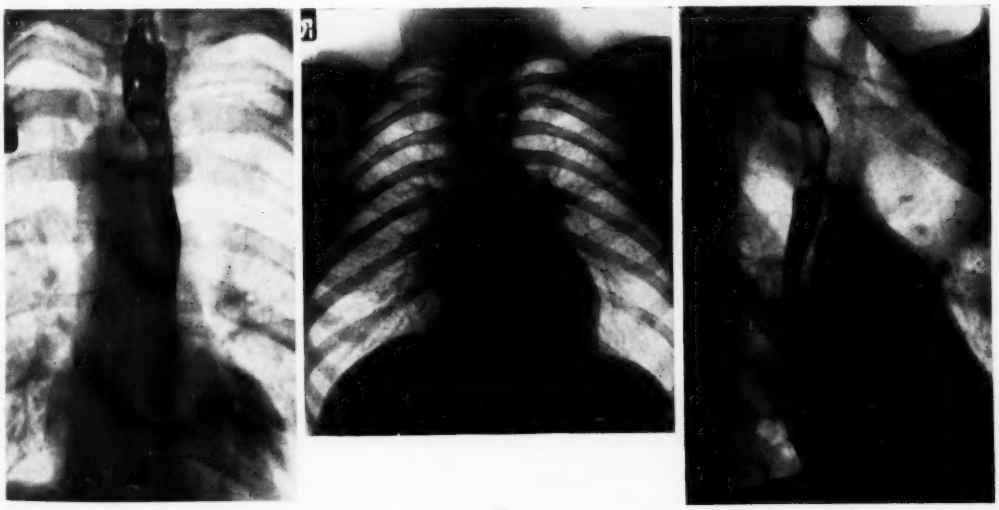
Among the causes of extrinsic pressure upon the trachea and main bronchi must be included abnormalities of the aortic arch and its branches. The presence of a syphilitic aortic aneurysm is well known as a cause of pressure on the trachea and left main bronchus, but in childhood and early adult life, as well as later, the possibility of congenital abnormalities should not be overlooked.

Case Report

A young man, aged 18, height 72 inches, weight 152 lb. underwent a medical examination late in 1955, prior to entry into the Police. Routine physical examination showed him to be of normal physique, with no skeletal or muscular abnormality. Nothing of note was made out on examination of his cardiovascular and respiratory systems, but he was found to be unduly dyspnœic on exertion, a fact that both the patient and his father had known for several years, and that had caused the patient to forego any strenuous activity. His father could easily outstrip him in a sprint.

Because of this dyspnœa he was referred to the Heart Clinic of the Liverpool Royal Infirmary for further investigation. Physical examination again revealed no abnormal features. The blood pressure in both arms was 110/85 mm. of mercury. The femoral pulses were normal. Examination of the heart disclosed no abnormality of size, sounds, or pulsations, and the lungs appeared healthy. No stridor was heard. The electrocardiogram was physiological. The blood count gave normal results and the urine contained no unusual constituents.

Radioscopy, however, revealed the presence of a right-sided aortic arch, the œsophagus being displaced anteriorly by a persistent left root (Fig. 1). Otherwise the cardiac outline was normal. Further investigation,



A B C

FIG. 1.—(A) Barium swallow in postero-anterior position, showing the right-sided aortic arch. (B) Showing postero-anterior radiogram. (C) Barium swallow in right anterior oblique, showing anterior displacement of œsophagus by persistent left root.

by bronchography and tomography revealed distortion of the trachea and right main bronchus, but attempts at angiography were unsuccessful. However, bronchoscopy and œsophagoscopy confirmed that the trachea was flattened on the right by a pulsatile swelling, which was also constricting the lumen of the right main bronchus to a mere slit. Oesophagoscopy showed a pulsatile swelling behind the œsophagus, pressure by the œsophagoscope producing obliteration of the left radial pulse.

Thoracotomy was undertaken on 8/3/56. Fig. 2 is a semi-diagrammatic appearance of the operative findings. The presence of a tight vascular ring around the trachea was confirmed, the right aortic arch

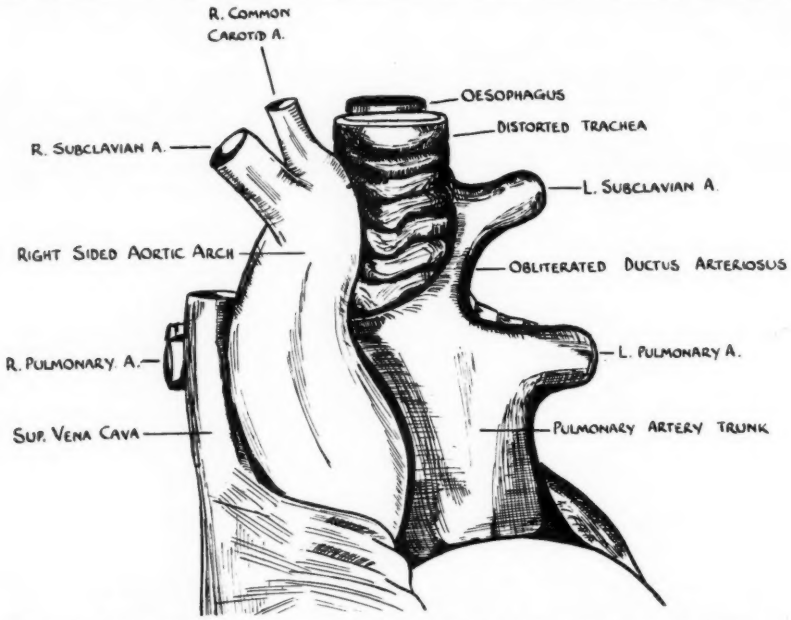


FIG. 2.—Appearance at thoracotomy, showing right-sided aortic arch, with persistent left root, from which the left subclavian arises. Note the tracheal distortion.

causing pressure on the right main bronchus and the trachea, the ring being completed by the pulmonary artery, and the short tough ligamentum arteriosum, which was attached to the persistent left root. All the main branches of the aorta were identified except the left common carotid which could not be located. The descending aorta was on the left.

The obliterated ductus was transfixed and divided; this at once relieved the pressure on the trachea and right main bronchus. Further dissection produced complete relief of pressure on the bronchus, and the pericardium over the pulmonary artery was fixed to the anterior chest wall, thus opening up the space still further.

Postoperative recovery was uneventful. Bronchoscopy three weeks later still showed tracheal distortion, but the right main bronchus was widely patent. Subsequent progress has been excellent; the patient is subjectively much better, and his exercise tolerance can now be regarded as normal.

Discussion

An excellent review of previously reported cases of abnormality of the aortic arch is given by Brown (1950) quoting extensively the classification of these abnormalities by Edwards (1948). Brown makes it clear that a right-sided aortic arch alone does not cause symptoms, especially when the descending aorta is on the same side. Even when the descending aorta is on the left, and a vascular ring is present, symptoms often only begin when degenerative changes in the aorta cause the pressure to become more severe.

Nevertheless, our case shows that where the vascular ring is narrow, symptoms may become manifest for the first time after childhood has passed by. Further investigation should b

undertaken, therefore, when a right-sided aortic arch is found in a patient complaining of dyspnœa for which no other cause can be found. In particular, angiography can be of great help, particularly where operative treatment is being considered.

Summary

A young man complaining of dyspnœa on exertion was found to have a right-sided aortic arch. At operation the trachea was found to be compressed by a tight vascular ring made up of the right aortic arch, the pulmonary artery, and the ligamentum arteriosum. Division of the obliterated ductus relieved the pressure and after operation the effort tolerance became normal.

The endoscopic examinations and the surgical treatment were performed in this case by Mr. L. J. Temple, to whom we are indebted for his help.

References

Brown, J. W. (1950). *Congenital Heart Disease*. London.
Edwards, J. E. (1948). *Proc. Mayo Clin.*, **23**, 108.
——, (1948). *Med. Clin. N. Amer.*, **32**, 925.

ABSTRACTS OF CARDIOLOGY

Edited in collaboration with Abstracts of World Medicine

Use of Mecamylamine in the Management of Hypertension. F. H. SMIRK and E. G. MCQUEEN. *Brit. med. J.*, **1**, 422, 1957.

The efficacy of mecamylamine ("inversine"), a secondary amine, in the management over a period of 4 to 8 months of 40 patients suffering from hypertension is discussed. Unlike the quaternary ammonium compounds pentolinium ("ansolysen") and chlorisondamine ("ecolid"), which are tertiary amines, mecamylamine is almost completely absorbed from the alimentary tract, so that the effective oral dose is little higher than the parenteral dose. Since the effect of mecamylamine lasts for over 12 hours, the drug is given in the present series of cases twice or occasionally 3 times a day. The average daily dose for satisfactory control of hypertension was 33 mg.; in no case did it exceed 70 mg. However, mecamylamine was more often associated with parasympathetic side-effects than either pentolinium or chlorisondamine, these side-effects causing considerable discomfort in 25 of the 40 patients. Constipation and abdominal distension were reported in 14 cases, dryness of the mouth in 11, nausea and vomiting in 9, and dysuria and blurring of vision in 5 each.

The authors point out that other secondary amines as yet untested may prove to be more satisfactory as ganglion-blocking agents than any of those which are at present available. *A. G. Freeman*

Renal Haemodynamic Effects of Hypotensive Drugs. I. Acute Effects of Hexamethonium Bromide before and after Treatment with Reserpine. B. GOLDBERG. *Lancet*, **1**, 74, 1957.

Hexamethonium was given intravenously to 13 hypertensive patients at the Middlesex Hospital, London, in doses sufficient to reduce the blood pressure with the patient in the recumbent position. During the fall of pressure the renal plasma flow fell, as also did urine flow and potassium and sodium excretion. Little significant alteration in these patterns of response took place when, in 5 cases, the hexamethonium was given during treatment with reserpine. At the height of the hypotensive effect of methonium salts there is usually renal vasoconstriction. This may be a consequence of vasodilatation and pooling of blood in the limbs leading to decreased cardiac output and diversion of blood from the kidneys. *J. McMichael*

Renal Haemodynamic Effects of Hypotensive Drugs. II. Effects of Oral Maintenance Therapy with Pentapyrrolidinium Bitartrate and Reserpine. L. MCDONALD and B. GOLDBERG. *Lancet*, **1**, 77, 1957.

The long-term effects of the oral treatment of hypertension with pentolinium and reserpine were observed at the Middlesex and National Heart Hospitals, London, in 6 patients, all but one of whom showed a satisfactory response of the blood pressure to the treatment. A slight lowering of the renal vascular resistance was observed, but the cardiac output and general renal hæmodynamic patterns were little changed. *J. McMichael*

Results of Nephrectomy in Hypertensive Patients. G. J. THOMPSON. *J. Urol.* (*Baltimore*), **77**, 358, 1957.

At the Mayo Clinic approximately 3000 patients were subjected to unilateral nephrectomy during the 15-year period 1940–54, and of these, 11 per cent were found to have hypertension. Of these 337 (194 females and 143 males), 39 had renal tumours, 119 an atrophied or hypoplastic kidney, while 179 suffered from miscellaneous renal conditions. A "good early effect" of nephrectomy was defined as a reduction in blood pressure to 140/90 mm. Hg, which was maintained when the patient was discharged from hospital. A "good late result" was recorded when the blood pressure remained below 140/90 mm. Hg for more than one year.

Of the 39 patients with renal tumours, a good early result was achieved in 12, but a year later only 5 had a normal blood pressure. Sympathectomy was performed in addition to nephrectomy in 29 cases—19 of atrophic pyelonephritis and 10 of other forms of unilateral renal disease.

When these 29 cases and 39 of renal tumour were excluded there remained 100 cases of atrophic pyelonephritis and 169 cases of other renal conditions for analysis of the results of nephrectomy in cases of hypertension. The results were better after nephrectomy in patients with atrophic pyelonephritis than in those with other forms of unilateral renal disease, a good early effect being obtained in 63 per cent compared with 38 per cent. After a follow-up period of one year or more the results were good in 35 of 64 patients suffering from atrophic pyelonephritis who were traced and in 25 of 100 with other renal conditions.

The authors conclude that nephrectomy should be performed on hypertensive patients suffering from severe unilateral renal disease, provided there are no other conditions which contraindicate operation. *L. G. Fallows*

Alveolar Walls in Mitral Stenosis. R. M. O'NEAL, W. A. THOMAS, K. T. LEE, and E. R. RABIN. *Circulation* (*N.Y.*), **15**, 64, 1957.

The extent and the character of the changes in the alveolar walls in mitral stenosis were studied in 95 cases seen at necropsy at Washington University School of Medicine, St. Louis, Missouri. Contrary to the observations of others, the authors found that the changes in

these cases were focal rather than widespread in distribution. Capillary dilatation was the commonest change, but even that was slight. The fibrous thickening of the alveolar walls, the thickening of the capillary basement membrane, and the cuboidal cells lining the alveoli, which have been noted by others, were seen in only a few cases of the present series and, when they did occur, were so focal in distribution as to make it unlikely that they could be of any physiological significance. The pathogenesis of these changes is briefly discussed.

J. B. Wilson

Necrotizing and Healing Pulmonary Arteritis with Advanced Mitral Stenosis. D. M. SPAIN. *A.M.A. Arch. Path.*, **62**, 489, 1956.

From the necropsy records of 26 patients dying of rheumatic fever at the Presbyterian Hospital, New York, the author has studied the relationship between rheumatic heart disease and necrotizing pulmonary arteritis. The lesions involved small and medium-sized vessels, especially at bifurcations. Active lesions showed fibrinoid or eosinophilic necrosis, with an intramural and perivascular inflammatory cell infiltrate which included only a few eosinophil granulocytes and no giant cells. Healed lesions were characterized by focal scars, the formation of new vessels in the arterial walls, and intimal fibrosis, the last named sometimes obliterating the arterial lumen; if recanalization occurred the condition resembled healed thrombo-embolism, but could be distinguished from the latter by the presence of focal scarring and the intramural new vessels.

Detailed analysis of these 26 cases revealed no correlation between the activity of the lesion and the activity of the rheumatic state, as judged by clinical or post-mortem findings. The only constant feature was the presence of severe mitral stenosis, and analysis of the records of 600 other cases of rheumatic heart disease showed that necrotizing pulmonary arteritis was never present in the absence of advanced mitral stenosis.

The author concludes that necrotizing pulmonary arteritis is not specifically rheumatic and that, since it is related constantly to advanced mitral stenosis, it is probably due to severe pulmonary hypertension.

M. C. Berenbaum

The Role of Valvular Incompetence in Heart Failure. J. MCMICHAEL and J. P. SHILLINGFORD. *Brit. med. J.*, 1, 537, 1957.

In this paper the part played by tricuspid incompetence in heart failure is reviewed. As tricuspid incompetence develops and increases in severity the fall in right atrial pressure which normally occurs with ventricular contraction (the "X descent"), as recorded by cardiac catheterization, is progressively lessened, obliterated, and replaced by a positive systolic pulsation. The amount of valvular incompetence can be estimated by recently devised dye-dilution methods. In 50 patients with various forms of heart disease with and without failure a remarkably close relationship was found between the level of the mean venous pressure and the development of functional tricuspid incompetence. The critical mean venous pressure was 8 mm. Hg above normal. This relationship held true except in constrictive pericarditis and conditions with very fast venous return, such as anæmia and thyrotoxicosis. In cardiac failure the aperture of tricuspid reflex may even become greater than that of the fully-open pulmonary valve, and the regurgitant flow may reach 6 to 7 litres a minute while the forward cardiac output is only 2 to 3 litres a minute. When the regurgitant stroke-output exceeds 40 ml. liver pulsation is obvious.

Exercise may actually decrease the forward output of the failing right ventricle, while increasing its total output. This probably explains the fixed or falling cardiac output which occurs with exercise in congestive failure, and may also explain the breakdown of Starling's law with rising venous pressure.

In view of these facts heart failure can no longer be clearly divided into "low-output" and "high-output" types.

D. Emslie-Smith

The Effect on the Left Ventricle of Surgical Closure of a Widely Patent Ductus Arteriosus. P. SOULIÉ, J. MATHEY, J. NOUAILLE, O. SCHWEISGUTH, P. VERNANT, P. CORONE, and G. O. OUSTRIÈRES. *Arch. Mal. Cœur*, **50**, 97, 1957.

The steep increase in the resistance to left ventricular outflow after closure of a patent ductus arteriosus may account for changes in the T wave of the electrocardiogram (EC) which sometimes follow this operation. In an infant of 7 months, closure of the duct was followed next day by severe left ventricular failure which was relieved only by direct aspiration of blood from the right ventricle. The EC 24 hours later showed the pattern of left ventricular stress. A less dramatic episode of failure occurred one week later. In 2 children aged 11 and 13 years respectively the effects on the left ventricle of closure of the duct were less startling. One showed changes in the EC on the 11th postoperative day; the other suffered tachycardia with systemic hypertension on the day following operation, and the EC revealed the pattern of left ventricular stress; improvement quickly followed the administration of digitalis, a mercurial diuretic, and reserpine.

The authors observe that awareness of the possibility of such developments will enable appropriate measures to be taken (1) in prevention, by avoiding excessive replacement of blood loss, and (2) in treatment, by immediate cardiac aspiration if no suitable vessels are accessible.

R. S. Stevens

The Electrocardiogram in Atrial Septal Defect. A Study of Twenty-four Cases, with Observations on the RSR′-V1 Pattern. W. R. MILNOR and C. A. BERTRAND. *Amer. J. Med.*, **22**, 223, 1957.

At the Johns Hopkins University Hospital, Baltimore, the authors have studied 24 patients in 7 of whom the diagnosis of atrial septal defect was verified at necropsy and in 17 at operation. Persistent ostium primum was diagnosed in 6 cases and ostium secundum in 18. Only 3 of the patients with persistent ostium primum, the 3 with a cleft in the aortic cusp of the mitral valve could be distinguished from the other 21 in that the EC in these

cases showed left axis deviation and signs of combined right and left ventricular hypertrophy—signs that are regarded as being due to the mitral incompetence.

In 22 cases there were signs of right ventricular hypertrophy and in 18 of right axis deviation. An RSR′ pattern in V1 was found in 15 patients (63%), with a QRS duration of 0·09 second or less in 5 cases, 0·09 to 0·12 second in 8, and 0·12 second or more in 2 cases. Regarding the controversial question whether an RSR′ pattern in V1 with a QRS duration of less than 0·12 second necessarily indicates delay in a bundle branch, the authors state their reasons for assuming that this pattern may represent a stage in the development of signs in the EC of right ventricular hypertrophy not necessarily associated with disturbances of conduction; in their view the term "incomplete right bundle-branch block" should be abandoned. The pattern of RSR′ in V1 is far commoner in atrial septal defect than in other clinically similar conditions and is thus of some differential diagnostic value, but the authors disagree with the statement of Barber *et al.* (*Brit. Heart J.*, 1950, **12**, 277) that "the diagnosis of atrial septal defect is almost untenable in the absence of partial or complete right bundle-branch block" since such an EC pattern was absent in 9 (37%) of this series of patients. *A. Schott*

Surgical Treatment of Aortic Stenosis. R. Brock. *Brit. med. J.*, **1**, 1019, 1957.

The author discusses the clinical features and surgical treatments of aortic stenosis with reference to the results of 120 operations carried out in such cases. Though conservative treatment is still often urged on the grounds that the expectation of life may be long, he thinks that this is only occasionally the case and that the condition may occur in comparatively young people. Out of 78 patients with severe symptoms, 31 were below 40 and 56 below 50 years old.

Assessment of the patient's clinical state should not depend on symptoms—the left ventricle is capable of a considerable degree of compensation and the presence of obvious symptoms may indicate the onset of failure. More exact measurement of the load on the heart must be obtained. The figures and curves obtained from comparison of the pressures in the left ventricle, measured by direct percutaneous puncture, and brachial artery give an actual picture of the pressure gradient across the stenosed valve, which is usually in the region of 50 mm. Hg, though it may reach double this figure. This should be confirmed at operation by direct puncture of the left ventricle and aorta. Apart from fusion of the valve cusps in aortic stenosis there is a considerable degree of distortion, and calcification is frequent. The rock-like valves that are sometimes encountered cannot be mobilized except at the risk of severe regurgitation, and it is doubtful whether "cure" is ever possible when the valves are calcified. Calcification is less common in aortic stenosis associated with mitral valvular disease, 20 out of 34 such cases in the author's series being free from this complication.

Combined mitral and aortic valvotomy was undertaken in 34 of the author's cases, with 3 operative deaths (due to the mitral lesion). In 12 cases the result was "good" or "excellent". Four patients have since died. There were 2 cases of aortic stenosis associated with coarctation, both lesions being severe.

Excluding 5 cases of subvalvular stenosis and one in which valvotomy was not carried out there were 78 cases of isolated aortic stenosis, some of which, particularly the early cases, being very bad risks. The over-all mortality was 18 per cent, but excluding the first 8 cases it was 13 per cent, and of the last 48 patients treated, only 3 have died. Of the 64 survivors, 9 have since died; the results in 42 can be classed as "good" or "excellent". Regurgitation following operation was observed in 14 cases and in 4 cases was responsible for later death, but in some cases preoperative regurgitation has been relieved. *T. Holmes Sellors*

OBSERVER VARIATION IN REPORTS ON ELECTROCARDIOGRAMS

BY

L. G. DAVIES*

From the Department of Medicine, Postgraduate Medical School of London

Received August 7, 1957

It is now well known that the results of almost any examination or investigation may be reported differently by different workers, for example, the interpretation of a medical history (Cochrane *et al.*, 1951), the detection of cyanosis (Comroe and Botelhoe, 1947) or clubbing (Pyke, 1954), the clinical diagnosis of emphysema (Fletcher, 1952), the radiological detection of tuberculosis (Birkelow *et al.*, 1947; Garland, 1950), and the assessment of pneumoconiosis (Fletcher and Oldham, 1949).

Disagreement may be due to true errors of observation where certain abnormalities are wrongly identified or even missed altogether. But in the investigation reported here, as in many others there is a second factor, the observation may be correct, but there is a difference of opinion about its interpretation. The term observer variation used in this paper is defined as including disagreements due to both causes, for they occur together and it is sometimes impossible to tell which is responsible. Because of this, observer variation is a better expression of the problem than the term observer error.

The practical significance of observer variation has often been disputed (Lancet, 1954) and only in radiology is its importance being accepted. With the single exception of a report by Sloan *et al.* (1952) on the detection of the third heart sound, the problem of observer variation in cardiology has not been studied. This is surprising, for an electrocardiogram might be expected to be as difficult to interpret as is a chest film. They are of equal importance in that one is as valuable in the diagnosis of heart disease as is the other in the diagnosis of pulmonary disease; and both are single investigations upon which diagnosis and treatment may largely depend. Yet the assumption appears to be that unlike the chest film, electrocardiography is a test free from observer variation. The purpose of this paper has been to test that assumption, and it has proved to be false. Not only has observer variation been found, but its extent was surprising and it has been possible to identify many of its causes. The practical significance of this variation will be discussed in the belief that it may often contribute to diagnostic errors.

Material and Methods

One hundred tracings were selected from the files of the Department of Cardiology at Hammersmith Hospital. They included 50 that had been reported to show infarction, 25 that had been reported as normal, and 25 that had been reported to show some abnormality other than infarction. The last group included right and left ventricular hypertrophy, myxœdema, pericarditis, the effects of electrolyte upset, and so on. In order to simplify reporting, only tracings that had been taken with the same photographic machine were selected. Each group formed a consecutive series except that tracings from children or those containing less than nine leads (standard and unipolar limb leads with V1, V3, and V5) were excluded. Arrhythmias when present were incidental. These tracings were then mixed together and given in turn to each of the following 10 observers:

Dr. L. G. Davies
Dr. B. D. van Leuven } .. .. Medical Registrars, Hammersmith Hospital.
Dr. T. B. Counihan

* Present address—National Heart Hospital, W.1.

Dr. Max Zoob	.. ..	Senior Medical Registrar, Hammersmith Hospital.
Dr. J. F. Goodwin	.. ..	Lecturer in Medicine, Hammersmith Hospital.
Dr. Fulvio Camerini	.. ..	World Health Organization Fellow, Hammersmith Hospital.
Dr. G. R. Venning	.. ..	Senior Medical Registrar, Manchester Royal Infirmary.
Dr. William Phillips	.. ..	Physician, Cardiff United Hospitals.
Professor I. G. W. Hill	.. ..	St. Andrews.

All the readers had special interest and experience in cardiology, three were consultants and the others were then of registrar or senior registrar grade. Their individual identities have been concealed behind alphabetical symbols (A to I—but not of course in the above order). Included for comparison are the results obtained by a tenth reader, J, who is an experienced physician with a wide knowledge of medicine, but has his special interests outside cardiology.

The composition of the series was explained and the readers given the choice of reporting each tracing as either normal, abnormal, or showing infarction. In view of the selection of the tracings this was thought to be reasonable and the observer was not asked to locate the infarct or identify the nature of the abnormality. Clinical details were not given as they might have caused bias and the investigation was concerned with the diagnostic value of a single electrocardiogram in its own right. The amount of time spent in reporting was left entirely to the reader and ranged from 45 minutes to 2 hours. After an interval of not less than a fortnight the readers were asked to report again on the same electrocardiograms. It was found unnecessary to alter the order of the tracings at this second reading for although an occasional one was familiar, the previous report could not be recalled.

It is assumed that no less time and care were given to reporting than would have been used in normal practice.

Results

The gross results are illustrated diagrammatically in Fig. 1. The number of tracings reported normal by the experienced observers ranged from 13 to 29, abnormal from 20 to 44, and infarction, from 36 to 63. These discrepancies were considerable and there was equal disagreement over each diagnosis. Observer J found twice as many infarcts the second time as he did the first but the

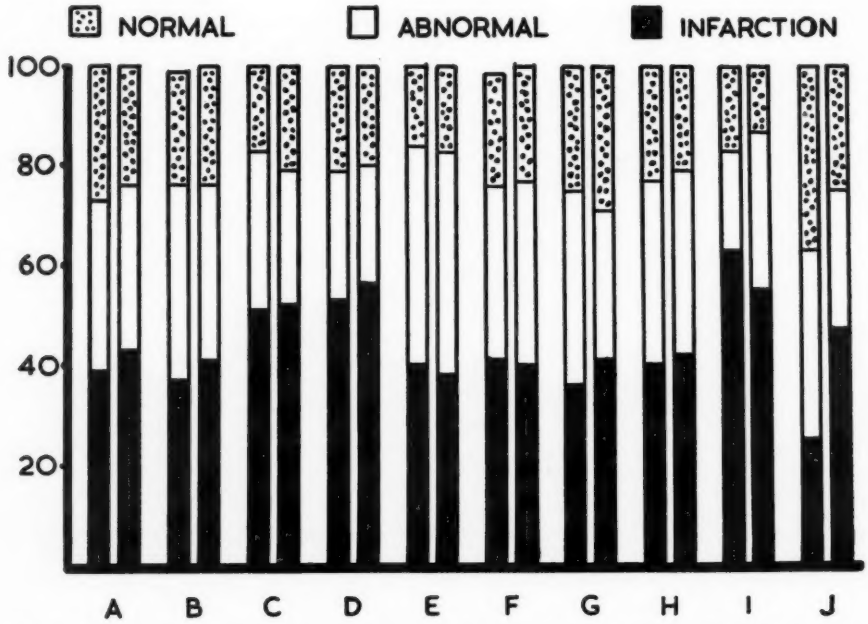


Fig. 1.—Each observer reported twice on the 100 electrocardiograms and this diagram shows the proportion reported each time as normal, abnormal, or showing evidence of infarction.

experienced observers appeared to be fairly consistent. This, however, was not the case, for instance the diagram does not indicate that the 14 tracings reported normal by E on his first reading are not all included in the 15 he reported normal on his second reading.

In fact after both readings by the 9 experienced observers there were only 29 tracings on which a unanimous report had been given. In 49 there was agreement by a majority arbitrarily defined as two-thirds. As each tracing had been reported on twice by the 9 experienced observers, each had collected 18 reports and a majority opinion was therefore 12 or more. It was usually much more, for in this group of 49 tracings there were 14 where there was only 1 disagreeing report, 6 where there were 2, 9 where there were 3, 8 where there were 4, 7 where there were 5, and 5 where there were 6 disagreeing reports.

In the remaining 22 tracings the dispute was greater than this and in a few of them opinion was almost evenly divided. In this group there was no satisfactory way of marking the results for there was no certain method of deciding who was right and who was wrong. It was impossible to accept the clinical diagnosis as dictating the correct electrocardiographic report for if the patient had rheumatic heart disease, angina, or hypertension, for example, the tracing could be normal or could be abnormal. But in the group of 49 tracings where there was majority agreement it seemed reasonable to assume that a large majority of 12 or more reports out of 18 was probably right and a small minority of 6 or less reports out of 18 probably wrong. Making this assumption, these tracings and the 29 where there was full agreement have been taken for further analysis.

These 78 tracings are then found to contain 19 that are normal or almost certainly normal, 20 that are " true abnormal," and 39 that represent " true infarction." Now each of the 9 experienced observers had reported twice on the 19 " true normal " tracings, a total of 342 reports: 292 of these were reports of normal, but there were 42 of abnormal and even 8 of infarction. So that even in tracings that are normal or almost certainly normal, there is still a 1 in 7 chance of a wrong report being given. This seems a large risk when the initial selection of the 100 tracings is recalled, especially when the 22 found most controversial have been excluded from this analysis. When the total reports on the true abnormal tracings were studied it was found that there was an almost equal chance of a " wrong " report of infarction being given; while a similar proportion of the true infarction tracings had been reported as merely abnormal. This variation is interesting and surprising though it may be claimed that error here is of less practical importance than the disagreement over the normal tracings.

The 156 reports on these 78 tracings show that this considerable dispute had not arisen as the result of large inaccuracies by one or two observers. In Table I each observer's report has been compared with the majority and presumably correct opinion.

TABLE I

DISAGREEMENT OF INDIVIDUAL OBSERVERS

Observer	A	B	C	D	E	F	G	H	I	J
Disagreements	7	19	25	11	24	12	9	16	25	56

For example, observer A disagreed with the majority in 7 reports out of 156 and was therefore probably wrong in these 7 reports. Although some observers did better than others the range is fairly close and all did much better than the inexperienced observer J who was apparently wrong in one report out of every three. Judged by this rough test, the three consultants as a group were no more accurate than the registrars.

It may be argued that the disagreements reported here are not genuine but are largely due to difference in terminology. For instance, one observer may report a tracing as showing infarction while another would consider it to be ischæmic and report it as abnormal. There is a little truth

in this, and as will be seen later the observers did differ in their definition of an infarction pattern. But in considering this objection the most important evidence lies in the personal changes of opinion between the first and second readings. These are shown in Table II.

TABLE II

CHANGES OF OPINION IN INDIVIDUAL OBSERVERS

Observer	A	B	C	D	E	F	G	H	I	J
Opinions changed in	11	16	19	7	16	13	10	10	18	33
Normal in one report, abnormal or infarction in the other	3	7	10	5	7	3	4	4	6	16
Consistency, percentage	89	84	81	93	84	87	90	90	82	67

For example, after observer A had reported a second time on the 100 tracings he was found to have changed his opinion on 11 of them. Indeed the experienced observers on average changed their minds over one tracing in every eight. Yet the range is fairly close and all did much better than J who disagreed with himself over one tracing in three. Again the consultants as a group were no more consistent than the registrars.

While it is possible therefore for differences in definition between one observer and another to cause apparent rather than real disagreement, it is obvious that whatever our definitions are they are certainly variable and inadequate, for they failed to prevent each observer from frequent disagreement with himself.

Are these personal changes of opinion of any importance? In Table II we see that in 3 of the 11 tracings over which observer A changed his mind, the report was altered from normal to some other report. Indeed, of the 120 occasions on which the 9 experienced observers changed their opinion, in 40 of them, that is 1 in every 3, the change was between normal and some other report. These changes must surely be highly important, they throw doubt on the diagnostic value of the electrocardiogram and the practical implications are considerable.

CAUSE OF DISAGREEMENT

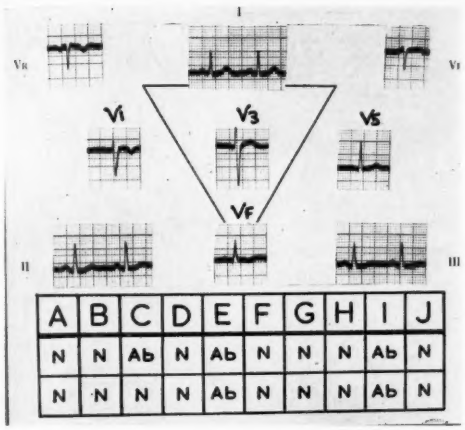
It is convenient to take the 78 tracings already described and consider the minority reports for these are almost certainly wrong. The lead or pattern that had caused disagreement could usually be identified, but this was not always the case and a few opinions were unaccountable. Obviously only a very few tracings can be included as illustrations.

Minor disagreement arose over most of the 19 true normal tracings. In 6 the configuration of aVL was responsible, in 4 the patterns in leads III and aVF (Fig. 2), in 2 the appearance of V3, in 2 the T wave contours, and in the other 2 the cause was not apparent.

In the group of 20 abnormal tracings there were 6 where leads III and aVF gave rise to difficulty and 3 where aVL was responsible. In the group of 39 true infarction tracings, there was disagreement in 9 where the infarct was posterior or postero-lateral and in 5 where it was anterior or antero-lateral. In three tracings there were T wave changes without abnormal Q waves (Fig. 3), and in two there was right bundle-branch block. In a further two tracings, the reasons for disagreement were not apparent.

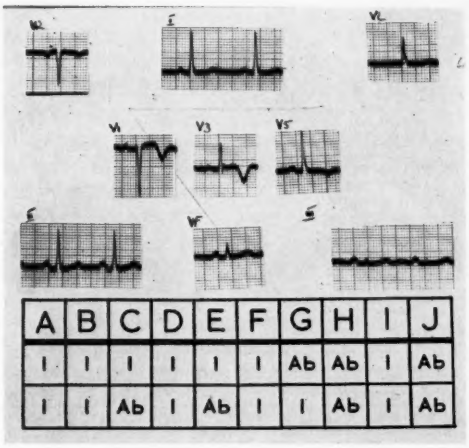
In summary the causes of disagreement are best related to particular leads and the greatest dispute was due to varying interpretation of leads III and aVF; there was also considerable uncertainty about the significance of QR or qR patterns in lead aVL.

It was more difficult to analyse the results in the 22 tracings where disagreement was considerable. In some of these, opinion was fairly evenly divided between normal and abnormal or between



A	B	C	D	E	F	G	H	I	J
N	N	Ab	N	Ab	N	N	N	Ab	N
N	N	N	N	Ab	N	N	N	Ab	N

FIG. 2.—In this and the following figures each observer's reports at the first and second reading are shown. There is some disagreement over this tracing but except for C the reports are consistent. The tracing has been classified as "true normal" on the opinion of a large majority and the contrary reports are almost certainly wrong. The cause of disagreement is the ST–T pattern in leads II, III, and aVF. The patient, a woman of 28 years, was admitted to hospital with no symptoms or signs of organic heart disease. Thyrotoxicosis was suspected but the various tests did not confirm this.



A	B	C	D	E	F	G	H	I	J
I	I	I	I	I	I	Ab	Ab	I	Ab
I	I	Ab	I	Ab	I	I	Ab	I	Ab

FIG. 3.—This graph is clearly abnormal but not all observers are convinced that it is diagnostic of infarction. Should infarction be reported in the absence of abnormal Q waves? This problem was an important cause of disagreement between observers and also a frequent cause of personal changes of opinion.

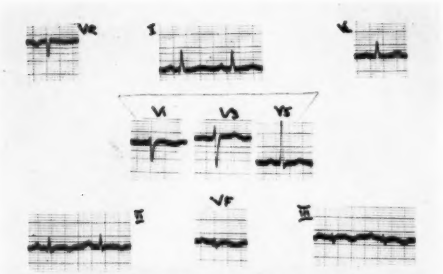
abnormal and infarction, but several tracings received all three alternative reports. Eight tracings came from patients where the clinical diagnosis or necropsy finding was myocardial infarction; in 6 of these 8 the lesion was posterior and difficulty was found in the interpretation of leads III and aVF (e.g. Fig. 4). The clinical diagnosis in this group of patients was supported by only 4 reports in every 7. The same leads caused confusion in three patients with hypertension and a further four with various diagnoses. Once again they stand out as the major cause of uncertainty and disagreement.

The configuration of aVL was the next most important cause, being wholly or partly responsible for dispute in four tracings (Fig. 5). Other causes were QS patterns in V3, the T wave contours in some præcordial leads, the size of the P wave, the P–R interval, and bundle-branch block. Four of the tracings were of rather poor technical quality and this may well have added to the other difficulties.

In fact, this group of 22 tracings was only quantitatively different from the others. The same difficulties were present, but in greater degree and sometimes in combination. This view is confirmed by finding that these 22 controversial tracings caused 52 personal changes of opinion while the remaining 78 caused only 101 changes. As might have been expected, the more likely a tracing is to cause disagreement between different observers, the more likely is it to lead to personal changes of opinion.

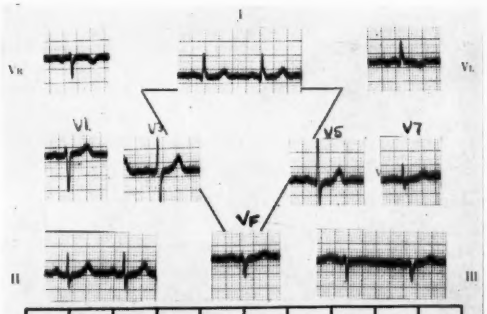
DISCUSSION

As there are now 22 English and American text books on the subject, electrocardiography must be considered an important branch of medicine. Graybiel (1951) writes in one that "a great responsibility is placed on the man who interprets electrocardiograms" and advises that he should



A	B	C	D	E	F	G	H	I	J
Ab	Ab	Ab	I	Ab	I	I	Ab	I	N
I	Ab	I	I	Ab	I	I	I	I	N

FIG. 4.—Leads III and aVF gave rise to disagreement more frequently than did any other leads. There was no general agreement as to what constituted an abnormal Q wave in these leads and criteria based on proportion are difficult to apply when, as in this tracing, the QRS voltage is low. A further difficulty was found to be the interpretation of Q waves in these leads when the T was upright.



A	B	C	D	E	F	G	H	I	J
N	N	N	I	Ab	N	N	N	I	Ab
N	Ab	N	I	N	I	N	N	Ab	N

FIG. 5.—Lead aVL was another frequent cause of dispute, as in this tracing. Each of the three alternatives were reported and there were frequent changes of opinion. This is one of the 22 tracings where the results cannot be marked for there is no strong majority opinion to determine the "correct" report. The patient, a woman of 59 with labile hypertension, complained of chest pain that was difficult to evaluate but finally was not accepted as cardiac.

"properly appraise his skill and avoid serious error." No suggestions are made as to how this should be done, nor indeed is any information given about the nature and incidence of errors. The results of this study confirm the validity of this warning yet the other text books contain no suggestions that there is ever any real difficulty in recognizing the different patterns from the descriptions given, and it is also implied that there is unanimous agreement between various authorities about their significance.

Disagreement not only exists, but in this trial was of surprising magnitude. In only a third of this group of tracings was opinion unanimous. In a half there was agreement by a majority of the readers, but this still left a substantial number—one tracing in five—over which there was considerable dispute. Moreover on second reading, the observers disagreed with one in every eight of their original reports. These findings are all the more remarkable when the initial selection of the tracings is recalled and our belief in the diagnostic value of a single electrocardiogram appears to be ill-founded. Other readers would be unlikely to improve on these results which must be taken as illustrating the difficulties of electrocardiographic diagnosis. And although these difficulties appear considerable, the experienced readers all did much better than the single inexperienced reader J.

It is very difficult to arrive at any accurate estimate of the practical importance of this observer variation. The prime use of the electrocardiogram is as an aid in the diagnosis of coronary disease and this is now so common that errors in diagnosis in even a small proportion of cases will affect large numbers of patients. The tracings used in this study were selected with this in mind. Yet in the group of 39 true infarction tracings there was unanimous agreement on less than half of them. Moreover, there were 7 tracings in the controversial group which received many reports of infarction. In none of the seven patients concerned was this thought at all likely, though in only two of them could this diagnosis be rejected with certainty.

It may be claimed that the electrocardiogram, although failing to give the correct answer in every patient with suspected infarction, is nevertheless always accurate enough when taken in conjunction with other evidence. Since diagnosis is made on the history and physical findings, supported by the results of special investigations, errors that might arise in each of these will be cancelled out when the results are considered together at a final diagnostic synthesis. This, at any rate, is the opinion of those who believe that observer variation is of no clinical importance (Lancet, 1954, and Pierce, 1954). This view I believe to be incorrect, for unless we study our diagnostic measures we shall fail to appreciate the extent and nature of the variation that may occur. Also the errors may not cancel out, they may summate, as in the following examples, where misinterpretation of the electrocardiogram contributed to major diagnostic errors.

For instance, in a report by Brumfitt and Rankin (1954) of a patient with chest pain, the electrocardiogram was thought to confirm the diagnosis of myocardial infarction and heparin was given. Two hours later the man died and necropsy showed a large dissecting aneurysm.

In another patient, also with pain believed to be due to myocardial infarction, electrocardiograms showed developing ST–T changes were interpreted as supporting this diagnosis (McCord and Taguchi, 1951). After several days treatment with anticoagulants the patient died and necropsy showed acute primary pericarditis with death due to hæmopericardium and tamponade.

A third example (personal observation) is that of a patient where myocardial infarction was diagnosed on the clinical picture and electrocardiographic changes. After further attacks of pain the correct diagnosis of repeated pulmonary embolism was made; later electrocardiograms—and in retrospect the earlier one—showed changes typical of right heart strain.

These examples illustrate the importance of observer variation in the interpretation of electrocardiograms in single clinical problems. But observer variation may be important in another way and in a wider field. In a discussion at the Royal Society of Medicine (1954) it was pointed out that the mortality in 11 separate series of patients with myocardial infarction varied between 13 and 45 per cent. The debate was over the value of anticoagulant treatment and it is not surprising that completely opposite opinions were expressed. It seems highly probable that differences in the criteria for diagnosing infarction could account for some of this wide scatter. The point is brought out in this study for when the extent of the disagreement emerged, each observer was asked to give his working definition for the recognition of infarction. These were surprisingly varied. One observer said he had reported infarction on S–T segment and T wave changes but most observers required the presence of abnormal Q waves. Some thought that large Q waves alone were certain evidence of infarction while others demanded T wave inversion as well. And then there was disagreement over the vital question of what constituted an abnormal Q wave, especially in leads III, aVF, and aVL. This dispute may seem surprising, but it seems clear that the distinction between infarction tracings and those showing lesser abnormalities is purely arbitrary; this point is not widely recognized and should be emphasized.

It is a matter of some interest that the observers had equal difficulty at the other end of the scale, in distinguishing between normal tracings and those showing minor abnormalities. The clinical importance of observer variation here is that misinterpretation of the electrocardiogram may lead to a diagnosis of heart disease in a person whose heart is in fact normal. Rosenbaum (1951) reported two instances where this had happened and his opinion was that one patient " may never recover," while Prinzmetal (1955) has referred to the existence of a syndrome that he calls " heart disease of electrocardiographic origin." The practical problem is the assessment of the chest pain so frequently present in Da Costa's syndrome, for slight changes in the S–T segment or T waves could, if wrongly interpreted, be taken to support an incorrect suspicion of heart disease. There are no figures that tell us how frequently this mistake is made, perhaps not as often as one wrong diagnosis in every seven subjects with healthy hearts; but this was the frequency of incorrect opinions on the true normal tracings. The objection that is always raised is that clinical error will not arise if the history, physical findings, and the tracing are considered together. But Evans (1952) has found the patient's description of his pain less reliable than the electrocardiogram,

some infarcts are painless (Lancet, 1954), and most patients with angina show no abnormal physical signs. Again electrocardiograms are now being demanded by some insurance companies as part of the medical examination. If the examiner believes he has found an abnormal tracing he is unlikely to accept the applicant's denial of symptoms. The advocates of the effort test (Master *et al.*, 1942, and Wood *et al.*, 1950) recognize that this diagnosis is often difficult and that a single electrocardiogram may be indecisive.

It follows that we should not expect the electrocardiogram to provide a clear division between normal and abnormal patterns; the range of both overlap and this to a greater extent than is commonly recognized. Distinction is least clear in leads III and aVF but there is also considerable difficulty with lead aVL. Tracings from the intermediate zones, where normal and abnormal or abnormal and infarction overlap are particularly liable to more than one interpretation and are most likely to give rise to changes of opinion. In clinical practice the interpretation would be very susceptible of bias due to the assessment of the history and other findings, and the dangers inherent in this mechanism have been illustrated. We should not expect too much of the electrocardiogram and it is time that we recognized that some tracings are of little diagnostic value.

Summary

The purpose of this paper was to show whether reports on electrocardiograms were subject to observer variation. A test series of 100 tracings was selected: half had been reported routinely to show infarction, a quarter to be normal, and a quarter to show various abnormalities other than infarction.

Nine experienced readers reported their opinions of these electrocardiograms on two separate occasions. They were allowed the choice of one of three reports—normal, abnormal, or infarction.

Complete agreement was reached in only one-third of the 100 tracings, majority agreement in half, but there was considerable dispute about one tracing in five. After the second reading, it was found that on average, the readers disagreed with one in eight of their original reports.

This considerable observer variation affected the normal, abnormal, and infarction tracings equally; it was much larger than had been expected and must represent the unrecognized difficulties of electrocardiographic diagnosis. Nevertheless the results obtained by these readers were all much better than those obtained for comparison by a single inexperienced observer.

The reasons for this large disagreement have been examined and the most important single cause was difficulty with the QRS–T pattern in leads III and aVF. There was also much uncertainty about the significance of QR patterns in aVL, and many minor causes.

From the standpoint of electrocardiographic diagnosis it is an illusion to believe there can be any arbitrary line between normal and abnormal tracings or between abnormal and infarction tracings. The ranges of each overlap and do so more widely than is generally realized; distinction is least clear in leads III and aVF. It is apparent that tracings from the intermediate zones are of little or no diagnostic value, but are very likely to be interpreted according to the clinical bias. In this way observer variation may add to diagnostic error. The clinical importance of this variation is debatable, but it is so large that in the absence of reliable information to the contrary, its importance cannot be denied.

I am greatly indebted to the readers for very willing co-operation and to Dr. C. M. Fletcher for much advice and encouragement.

References

Birkelow, C. C., Chamberlain, W. E., Phelps, P. S., Schools, P. E., Zacks, D., and Yerushalmy, J. (1947). *J. Amer. med. Ass.*, **133**, 359.
Brumfitt, W., and Rankin, N. E. (1954). *Lancet*, **2**, 792.
Cochrane, A. L., Chapman, P. J., and Oldham, P. D. (1951). *Lancet*, **1**, 1007.
Comroe, J. H., and Botelho, S. (1947). *Amer. J. med. Sci.*, **214**, 1.
Evans, W., and McRae, C. (1952). *Brit. Heart J.*, **14**, 492.

Fletcher, C. M. (1952). *Proc. Roy. Soc. Med.*, **45**, 577.
—— and Oldham, P. D. (1949). *Brit. J. Indust. Med.*, **6**, 168.
Garland, L. H. (1950). *Amer. J. Roentgenol.*, **64**, 32.
Graybiel, A., (1951), see *Clinical Heart Disease*, by S. A. Levine, London.
Lancet Annotation (1954). **1**, 87, and **2**, 799.
McCord, M. C., and Taguchi, J. T. (1951). *Arch. intern. Med.*, **87**, 727.
Master, A. M., Friedman, R., and Dalk, S. (1942). *Amer. Heart J.*, **24**, 777.
Pierce, J. W. (1954). *Lancet*, **1**, 737.
Prinzmetal, M. (1955). Cardiac Society Meeting, San Francisco.
Proc. Roy. Soc. Med. (1954), **47** 317.
Pyke, D. A. (1954). *Lancet*, **2**, 352.
Rosenbaum, F. F. (1951). *Ann. intern. Med.*, **35**, 542.
Sloan, A. W., Campbell, F. W., and Steward-Henderson, A. (1952). *Brit. med. J.*, **2**, 853.
Wood, P., McGregor, M., Magidson, O., and Whitaker, W. (1950). *Brit. Heart J.*, **12**, 363.

Editorial Comment

If anyone thinks that a report on a single electrocardiogram can always decide whether it is normal or abnormal or whether there is or is not evidence of cardiac infarction, this valuable paper will show that he is wrong. No one, on reflection, does think this, but many write a routine report as if they did.

Those asked to report were given only the three choices and not allowed to give more borderline reports, and this could be criticized. It may be argued that some doubt about the validity of the report is tacitly assumed by everyone, but this is not so. Everyone should be more aware that although some electrocardiograms are obviously normal and others prove cardiac infarction, there are many that could be normal but should raise a suspicion of coronary disease, many that prove some myocardial disease and raise a suspicion of cardiac infarction, and many with something unusual that might be due to heart disease or biochemical changes. It seems clear from this paper that more such qualifications should be added to reports on electrocardiograms whenever these are needed.

THE USE OF AMYL NITRITE IN DIFFERENTIATING MITRAL AND AORTIC SYSTOLIC MURMURS

BY

JOHN BARLOW AND JOHN SHILLINGFORD*

From the Department of Medicine, Postgraduate Medical School of London

Received August 21, 1957

The clinical differentiation of the apical systolic murmurs arising at the mitral and aortic valves may be difficult. This is especially so when the murmur of aortic origin is audible only at the apex or is loudest at this site.

Phonocardiography gives further help in that the murmur of aortic stenosis is diamond shaped and ends before the aortic second sound while that of mitral regurgitation is pansystolic and often includes the second heart sound (Leatham, 1951; Besterman, 1955). Where phonocardiography is not available the distinction has to be made on clinical auscultation alone.

The purpose of this paper is to show that the inhalation of amyl nitrite has a different effect on these two murmurs and is therefore useful in their differentiation.

Clinical Observations

During the first fifteen to twenty seconds after the inhalation of amyl nitrite, the murmur of mitral regurgitation diminishes in intensity and duration: these changes last for at least twenty seconds and thereafter the murmur returns to its original state. The ejection systolic murmur of aortic origin, however, remains unchanged, or increases slightly, during the first twenty seconds then increases to a maximum intensity twenty-five to forty seconds after the inhalation: the murmur then fades and has usually returned to its original intensity 60 to 70 seconds after inhalation of the drug. Where the apical systolic murmur is due to a combination of aortic and mitral valve disease, the regurgitant component fades during the first fifteen to twenty seconds whereas the ejection component increases twenty-five to forty seconds after inhalation.

This clinical test has been applied in over a hundred patients with suspected mitral or aortic valve disease and has, we think, contributed towards an accurate diagnosis. In order to illustrate the effectiveness of the test, however, we selected a group of patients in whom the clinical diagnosis was firmly established on other grounds and recorded the changes produced by amyl nitrite on phonocardiograms.

Phonocardiographic Observations

Thirty patients were studied; ten had definite clinical signs of mitral regurgitation, ten of aortic stenosis, and ten mixed mitral regurgitation and aortic stenosis. An apical phonocardiogram at medium frequency with a simultaneous electrocardiogram was recorded in each patient before the administration of amyl nitrite and every ten to fifteen seconds afterwards for a least two minutes: the tracings were made in expiration.

The phonocardiographic findings are summarized in Table I. Where there was no significant change in the systolic murmur, the result was recorded as negative, but changes in the murmurs were divided into slight, moderate, or marked. In the mitral regurgitation group a positive response was

* Member Scientific Staff, Medical Research Council.

TABLE I

CHANGES IN SYSTOLIC MURMURS AFTER THE ADMINISTRATION OF AMYL NITRITE, AS SHOWN BY PHONOCARDIOGRAPHY

Mitral regurgitation	No.	Negative	Positive		
		No significant change in SM	Decrease in length and intensity of systolic murmur (S.M.)		
			Slight	Moderate	Marked
Sinus rhythm	6	0	2	2	2
Auricular fibrillation	4	0	2	2	0
Total	10	0	4	4	2

Aortic stenosis	No.	Negative	Positive		
		No significant change in SM	Increase in intensity of SM		
			Slight	Moderate	Marked
Sinus rhythm	10	0	3	6	1
Auricular fibrillation	—	—	—	—	—
Total	10	0	3	6	1

Mitral regurgitation and aortic stenosis	No.	Negative	Positive		
		No significant change in SM	Early decrease and late increase in intensity		
			Slight	Moderate	Marked
Sinus rhythm	7	1	2	3	1
Auricular fibrillation	3	2	1	0	0
Total	10	3	3	3	1

accepted when the phonocardiogram showed a significant decrease in the intensity and length of the murmur (Fig. 1 and 2): in all ten cases this result was achieved to varying extent. Conversely, in the group with aortic valve disease a positive result was recorded when the systolic murmur increased after amyl nitrite (Fig. 3): again all ten cases produced a positive response. In the third group of patients with combined mitral and aortic valve lesions the phonocardiographic interpretation was more difficult. A positive response was accepted if the systolic murmur diminished in intensity and duration during the first twenty seconds but then increased to an intensity greater than that of the control record between 25 and 40 seconds. During the first twenty seconds the shape of the murmur tended to become more of the ejection type, presumably due to fading of the regurgitant component. The subsequent increase in intensity after 25 seconds occurred in early or mid systole as would be expected with an increase of the aortic component (Fig. 4). A positive response occurred in seven out of ten cases in this group.

In addition to the specific changes in the murmurs the amyl nitrite usually caused a tachycardia and invariably produced an increase in the first, and a decrease in the second, heart sound.

DISCUSSION

On clinical auscultation of forty-eight patients with mitral regurgitation, Kahler (1932) observed that after the administration of amyl nitrite there was a decrease or disappearance of the systolic

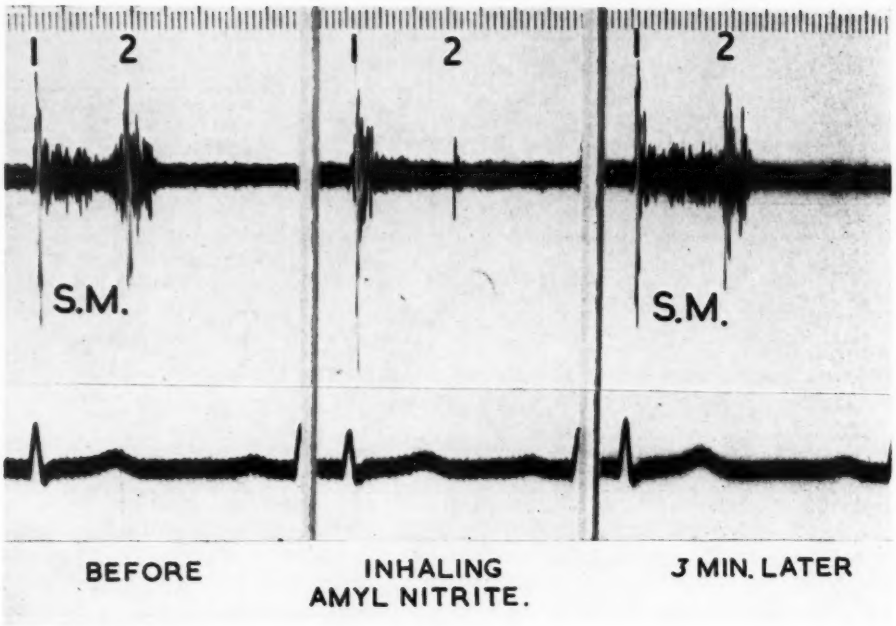


FIG. 1.—The effect of the inhalation of amyl nitrite on the murmur of mitral regurgitation, showing decrease in systolic murmur and second sound with increase in the intensity of the first sound.

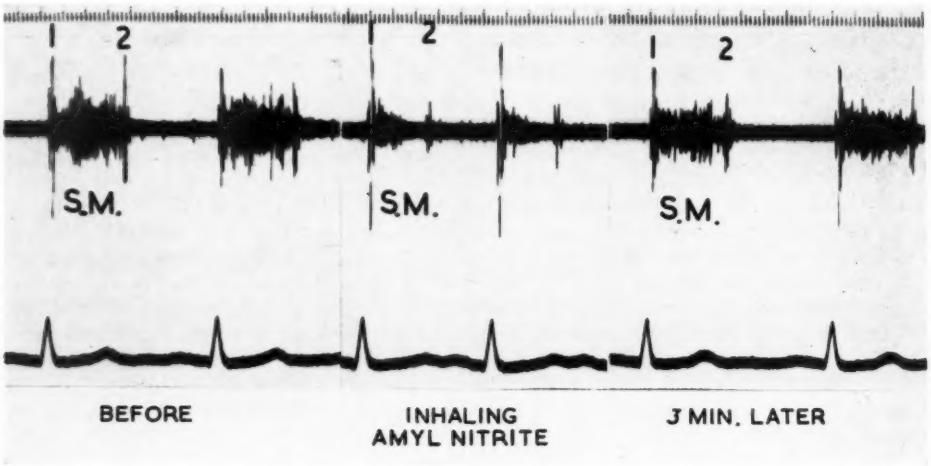


FIG. 2.—The effect of the inhalation of amyl nitrite on the murmur of mitral regurgitation. Note disappearance of murmur in late systole and around the second sound.

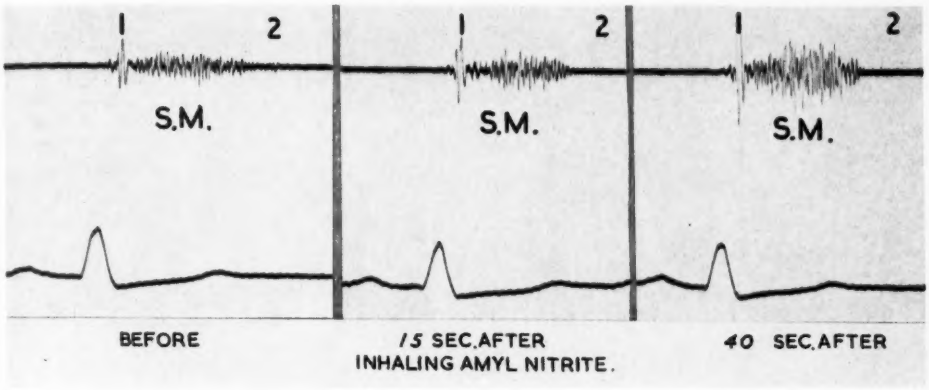


FIG. 3.—The effect of the inhalation of amyl nitrite on the murmur of aortic stenosis, showing progressive increase of systolic murmur up to 40 seconds.

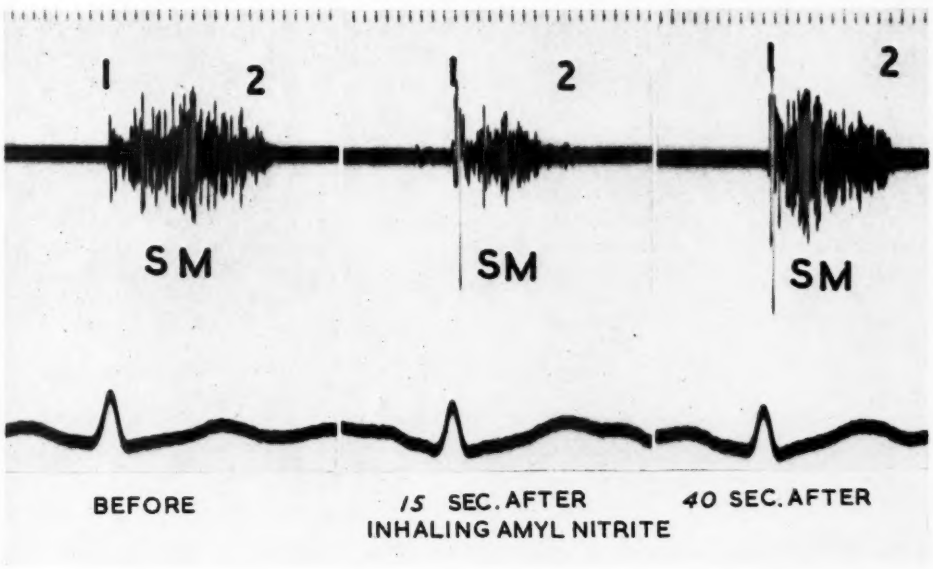


FIG. 4.—The effect of inhaling amyl nitrite on the combined murmurs of aortic stenosis and mitral regurgitation. See text for description of changes.

murmur in forty-four cases, while in the remaining four the murmur was unchanged. He considered that this feature differentiated the murmur of mitral regurgitation from most functional ("akzidentellen") systolic murmurs which increased with amyl nitrite. Friedlander and Brown (1935) produced transient systolic murmurs with this drug in forty-seven of a hundred patients with normal hearts and Mannheimer (1955), who demonstrated an increase of the "physiologic" systolic murmur in children on phonocardiograms, was of the opinion that the change was due to an increased cardiac output.

While we have found amyl nitrite of use in the clinical differentiation of apical systolic murmurs at the bedside, there are certain conditions under which a correct interpretation of its effect may be difficult. In auricular fibrillation a systolic murmur varies in intensity and duration and this makes the changes produced by amyl nitrite difficult to assess. An overall effect may be apparent on a phonocardiogram when numerous beats are compared, but, unless the change is marked, this is unreliable or impossible on clinical auscultation.

It might appear that the changes shown on the phonocardiogram in a combined aortic and mitral lesion (Fig. 4) would be difficult to appreciate by auscultation. However, whereas a phonocardiogram will only show a change in intensity and duration of the systolic murmur, on clinical auscultation it is also possible to discern alterations in pitch and quality. In addition, we have found that by auscultation outside the apex towards the axilla where the regurgitant component predominates, its fading in the first fifteen to twenty seconds before the increase of the ejection component is more readily appreciated. Auscultation at the apex itself, where the systolic murmur is usually loudest, may be misleading if the ejection component predominates to such an extent that the fading of the regurgitant component is difficult to discern. Where it is suspected that the murmur is arising from both aortic and mitral valves, a more accurate interpretation of the effect of amyl nitrite may be obtained if there are two observers, one listening at or inside the apex, and the other outside the apex towards the axilla. The latter will hear the regurgitant murmur fade within the first twenty seconds whereas the former will hear the ejection component increase between 25 and 40 seconds approximately.

The mechanism of the reduction in the intensity of the systolic murmur in mitral regurgitation by amyl nitrite may be due to the lowering of the peripheral resistance which allows a relatively greater part of the stroke volume to pass forward through the aortic valve. In the absence of other hæmodynamic data, however, this can only be speculative. Similarly the increase in the aortic systolic murmur may be due to an increased stroke output.

Summary

The effect of the inhalation of amyl nitrite on the apical systolic murmurs of mitral regurgitation and aortic stenosis is described.

It is shown that amyl nitrite decreases the intensity of the murmur of mitral regurgitation but increases that of aortic stenosis.

Its value in clinical practice is discussed.

References

Besterman, E. M. M. (1955). *Brit. Heart J.*, **17**, 360.
Friedlander, R. D., and Brown, M. G. (1935). *Ann. intern. Med.*, **8**, 893
Kahler, H. (1932). *Wien Arch. inn. Med.*, **23**, 349.
Leatham, A. (1951). *Brit. Heart J.*, **13**, 153.
Mannheimer, E. (1955). *Advanc. Pediat.*, **7**, 171

THE ORTHOGONAL ELECTROCARDIOGRAM IN LEFT VENTRICULAR HYPERTROPHY

BY

E. J. FISCHMANN

From the Cardiology Department, Green Lane Hospital, Auckland, New Zealand

Received March 26, 1957

It has been shown experimentally that three bipolar electrocardiograms from the main axes of the body contain as much or more information about QRS forces than 12-lead electrocardiograms (Frank *et al.*, 1955; Schmitt and Simonson, 1955; and Newman *et al.*, 1955). A clinical comparison of such a three-lead system and the 12 conventional leads has not yet been reported, and one aim of the present study is to make this comparison in left ventricular hypertrophy (LVH).

The three leads under discussion have been used mainly in the synthesis of vector loops. It was shown previously (Fischmann and Brown, 1954; Fischmann, 1955) that much of the behaviour of the spatial vector loop is revealed by inspection of these three leads recorded with a conventional electrocardiograph. To demonstrate this in left ventricular hypertrophy is another aim of the present study.

The description of normal leads in the present paper is incomplete, as the boundary between normal and abnormal conditions other than in left ventricular hypertrophy is not drawn. While a two-channel electrocardiograph was used throughout, useful information may be obtained by single-channel recording.

Material and Method

A hundred and nineteen normal subjects and 42 abnormal subjects were studied. The abnormal group consisted of 4 patients with aortic regurgitation and radiological evidence of cardiac enlargement, and 38 patients in whom repeated estimations over several months have shown that the diastolic pressure was 100 mm./Hg or more. Selection was not affected by radiological or cardiographic evidence of LVH in hypertension or cardiographic evidence of LVH in aortic regurgitation. None of the subjects studied had evidence of ischæmic heart disease, none were under drug therapy, and none showed branch block or an " X " wave in either lead V1 or V2. All were ambulatory and over 20 years of age.

A frontal plane lead-pair (vertical and transverse lead of the Duchosal-Grishman " cube "), and a horizontal plane lead-pair (sagittal and transverse lead) were recorded with a two-channel electrocardiograph (Fischmann and Brown, 1954). The transverse lead was the lower lead of each lead-pair, and served also as a common time base. The lead connections of Shillingford and Brigden (1951) were used; positive deflections in the vertical lead correspond to upward, in the transverse lead to leftward, in the sagittal lead to forward directed cardiac forces. To facilitate visualization the direction is marked in the illustrations, and the lead notation previously used (Fischmann and Brown, 1954) has been replaced by the letters *v* (vertical), *t* (transverse), and *s* (sagittal). These letters are also used in the text for the identification of the deflections (e.g. R*t* means the R wave of the transverse lead). In the vertical lead, positive and negative mean above and below the isoelectric line, without reference to the Einthoven standard lead polarity convention. QRS deflections and S–T deviation in the three leads of all subjects were measured using magnification where necessary and tabulated on a master chart, together with a qualitative description (positive, negative, diphasic, isoelectric) of the T wave. Amplitudes measured in mm., were divided by the amplitude of the calibration excursion (approximately 1 mV=1·5 cm.) giving voltage in mV. From the

master chart minima, maxima, and means of some QRS wave, and composite voltages and wave ratios were then determined, and QRS configurations noted. Finally the LVH criteria of Sokolow and Lyon (1949) and Goldberger (1949) were applied to the 12-lead electrocardiograms of the abnormal group.

Results

Vertical Lead. Three forms of QRS were encountered in this lead. (1) Mainly negative QRS (rS, rSr', Qr) frequently found both normally and in LVH (Fig. 1). An abnormal variant could not

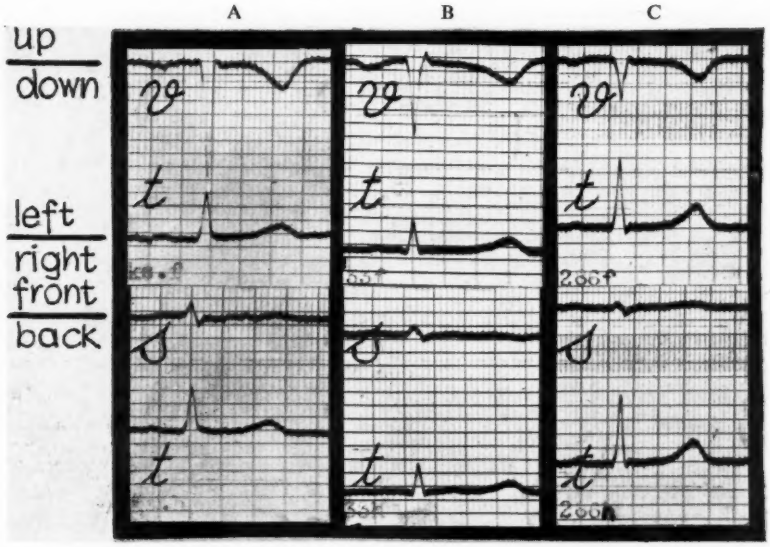


FIG. 1.—*Vertical lead QRS mainly negative, transverse lead QRS mainly positive, sagittal lead QRS symmetrical diphasic* (RS), as found in the majority of normal subjects and in some with LVH. (See Table I for incidence). Three normal records. *v*, vertical; *t*, transverse; *s*, sagittal lead. Thus R*v*=R wave of vertical lead. *Vectors:* Cardiac depolarization forces, which correspond to the main QRS deflection, are down (lead *v*) and left (lead *t*) directed.

be defined. (2) Mainly positive QRS (qR), rare in normals and common in the abnormal; with R wave in excess of 0·4 mV and R/Q ratio of 3 or more found only in the abnormal group (Fig. 2). (3) Bizarre QRS seen in the abnormal group alone (Fig. 5). S–T elevation of 0·05 mV and S–T depression in excess of this were seen in both groups, S–T elevation of over 0·05 mV in abnormals alone. All normal subjects except three in whom QRS voltage was less than 0·5 mV, showed negative T waves. Isoelectric T in the presence of QRS voltage greater than 0·5 mV, and diphasic T, were found in abnormal subjects alone. The voltage of the R wave in LVH at times exceeded the normal maximum R*v* voltage.

Transverse Lead. QRS configuration was remarkably constant in this lead, R being the greatest deflection in all normal and abnormal records. The S–T segment was isoelectric, or elevated by 0·05 mV or less, T always upright, in normals. S–T depression greater than 0·05 mV and negative, isoelectric or diphasic T occurred only in the abnormal. A comparison of the wave voltages of the QRS complex showed no useful difference between normal and abnormal.

Sagittal Lead. Four forms of QRS were encountered in this lead. (1) Symmetrically diphasic QRS with initial positive and terminal negative deflection (RS), common in both normals and the abnormal group (Fig. 3). An abnormal variant could not be defined. (2) Diphasic QRS with

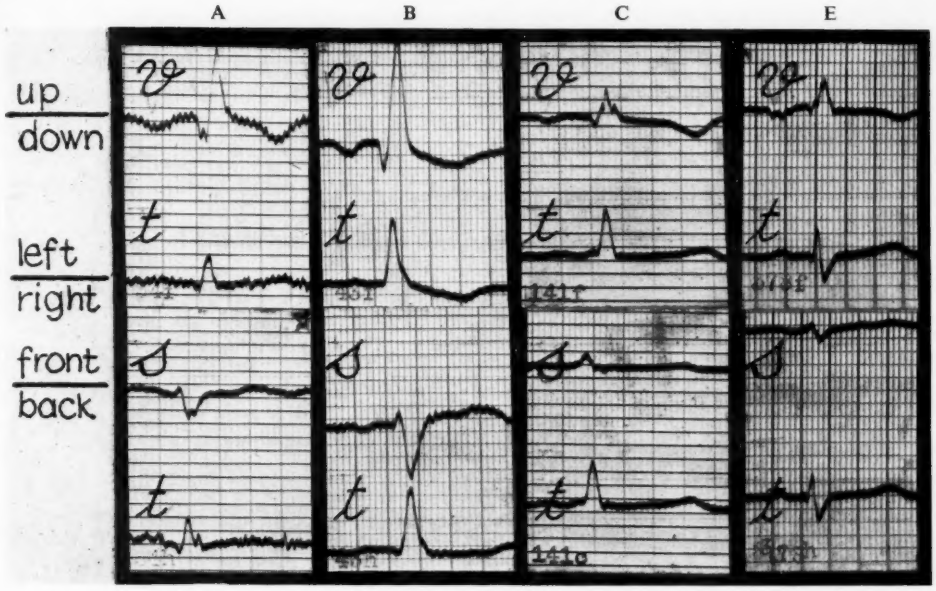


FIG. 2.—*Vertical lead QRS mainly positive*, as seen in 7 of 119 normals and in 16 of 42 subjects with LVH. Records of 4 abnormal subjects are shown. In LVH R*v* exceeds 0·4 mV or vertical lead R/Q ratio of 3 is exceeded. Transverse lead S–T and T abnormal in B. *Vectors:* In record C depolarization forces are up, left and backward directed, almost through the whole of QRS, in the other records shown they are so directed only in the latter part of QRS.

prominent R (Rs), rare in both normals and the abnormal. An abnormal variant was also not distinguishable. (3) Diphasic QRS with prominent S (rS), common in the abnormal and less common in normal; with an S wave in excess of 0·45 mV and an S/R ratio in excess of 6 only in the abnormal group (Fig. 3). (4) A QS pattern (Fig. 5B) was seen in two subjects of the abnormal group. Of the waves of the QRS complex S alone showed a useful difference between the normal and abnormal voltage range. In view of the relatively low voltage and the unsteady baseline in this lead the S–T segment was of no diagnostic value. Positive and negative T waves occurred in both normal and abnormal subjects.

Composite voltage measurements were calculated and R*v*+R*t* and R*t*+S*s* were significant; the former showed an upper normal limit of 1·3 mV was exceeded in 5 cases, and the latter showed an upper normal limit of 1·5 mV which was exceeded in two abnormal subjects: all of these 7 subjects showed other abnormalities in one or more of the three leads.

Vectorcardiographic data obtained by inspection and correlation of the three leads. This attempts to show, without assessing the incidence and validity of diagnostic criteria, that the behaviour of QRS and T vectors and vector loops in LVH is evident from the 3 leads. The spatial QRS vector loop in LVH (Duchosal and Sulzer, 1949; Scherlis *et al.*, 1951; Gardiner and Lowe, 1953; Horan *et al.*, 1954; Portheine, 1955; Wenger, 1955) is left, up, and backward orientated; its frontal projection often wide and inscribed counterclockwise; in the horizontal plane the loop may be wide and is normally inscribed. Frequently only the later portions of the loop are upward (Gardiner and Lowe, 1953). Wolff *et al.* (1953) found counterclockwise rotation round the long axis of the heart the most constant change in LVH. This resulted in an exaggerated disposition of initial forces right and forward and with reduced upward direction. The T loop in LVH deviates from the QRS loop and there may be a shift of the junction J.

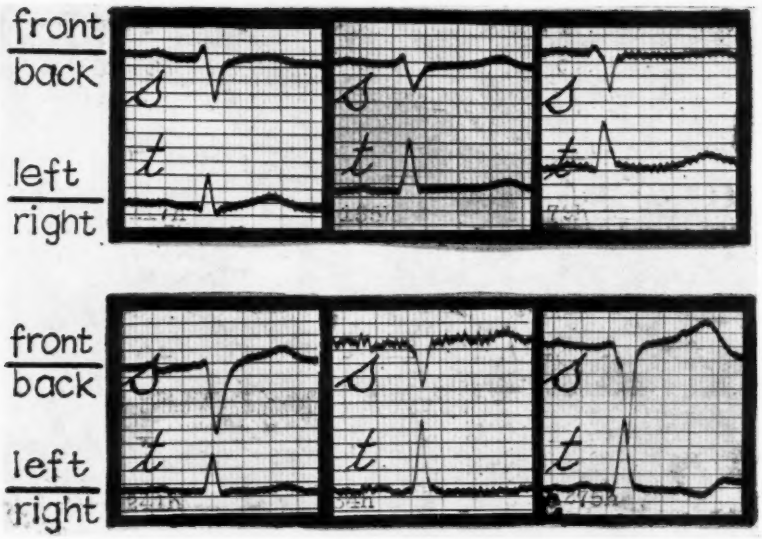


FIG. 3.—*Sagittal lead QRS mainly negative*, as seen in 20 of 119 normal subjects and in 28 of 42 with LVH. Horizontal plane (*s*, *t*) lead-pairs of three normal subjects (first row) and of three with LVH (second row) are shown. Abbreviations as Fig. 1. In the sagittal lead the S wave exceeds 0·45 mV (Calibration approximately 1·5 cm./mV) and the S/R ratio exceeds 6, in abnormal subjects only. Transverse lead S–T and T are abnormal in the last two records.

Fig. 4 shows lead-pair records in up, left and backward *orientation* of the QRS loop. In th first two records of the figure, the lateness of the R*v* and Q*s* peaks shows that up and backwar displacement affected mainly the latter parts of the loop, whereas asynchronism of the main QR peaks in these records shows increased *width* of both the frontal and horizontal plane loops. Thi may be compared with the normal records in Fig. 1, where near-synchronous or synchronous peak indicate narrow QRS loops (Fischmann and Brown, 1954). In all frontal plane (*v*, *t*) lead-pair of Fig. 2 and 4 the peak of R*t* (left), precedes the R*v* (upward) peak. This means that the directio of inscription in at least the distal part of the QRS loops was first left then upward, *i.e.* counte clockwise. In all records of the normal and in all but two of the abnormal group, initial QRS vector were forward directed, shown by the initially positive sagittal lead QRS. In addition the initi vectors were directed to the right, giving rise to a small q wave in the transverse lead (Fig. 2A; Fig. 4 or leftward, causing transverse lead QRS to commence with the upstroke of R (Fig. 1A and 5B Upward orientation of the initial vectors causes a small initial r wave in the vertical lead (Fig. 1B whereas downward initial vectors correspond to a q or Q wave in this lead (Fig. 2). Divergence the QRS and *T loops* causes discordance of the main QRS deflection and the T wave, in one or mo of the three leads, abnormal shifts of the junction J cause the S–T segment abnormalities describe in the preceding section.

DISCUSSION

Of the 42 abnormal subjects 37 showed the signs of left ventricular hypertrophy described b Sokolow and Lyon (1949) and 33 showed the criteria described by Goldberger (1949). In the thr leads of the " cube " system, 34 abnormal subjects presented changes not encountered in the norm (Table I). 31 of the 34 subjects showing changes in the " cube " leads also showed LVH in th

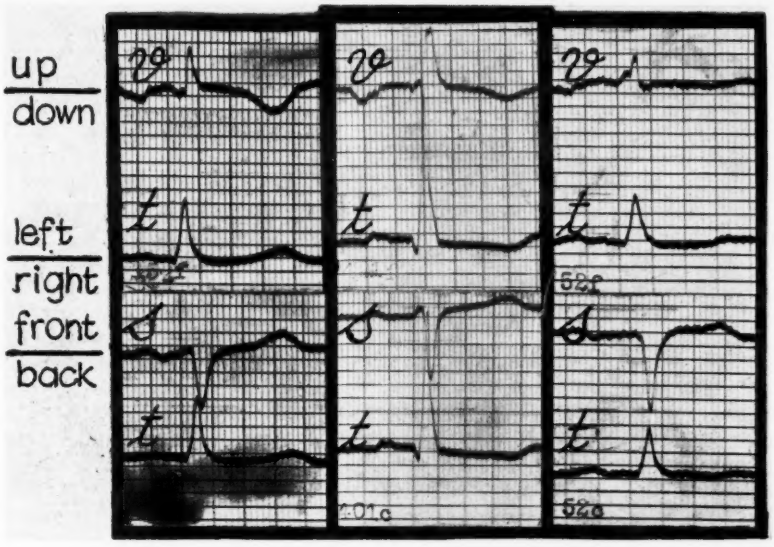


FIG. 4.—*QRS in vertical lead mainly positive, in sagittal lead mainly negative.* 3 records from subjects with left ventricular hypertrophy, combining the QRS anomalies shown in the two preceding Figs. Abbreviations as Fig. 1. Calibration approximately 1·5 cm./mV. Abnormal transverse lead S–T depression with T inversion in the second and with abnormal isoelectric T in the third record. *Vectors:* Depolarization forces corresponding to the main QRS deflection are up, left and backward directed. Initial forces in the two first records are down, right and forward, in the last record up, right and backward. A wide horizontal (*s*, *t*) plane QRS loop is indicated by asynchronism of the sagittal and transverse lead main QRS peaks. The frontal (*v*, *t*) plane vector loop is counter-clockwise inscribed in all records, as R*t* (leftward) precedes R*v* (upward). The orientation of the T wave in the last two records is abnormal: right and forward.

12-lead electrocardiogram. In spite of the disadvantages of the transverse lead of the " cube " system, the incidence of LVH changes in the three leads is comparable with the incidence in the conventional cardiogram. In addition the three leads supply information concerning the vectorcardiogram.

Apart from the initial and at times the terminal phases of ventricular depolarization, QRS forces are normally left and downward directed. In left ventricular hypertrophy, increase of the muscle mass and rotation of the heart around its longitudinal and anteroposterior axes, may displace these forces up and backward. If left ventricular activation is delayed by impairment of intraventricular conduction, left ventricular forces are unopposed by the normally partly synchronous, down and forward directed, right ventricular forces. This again will facilitate up and backward deviation of QRS forces. As a result of cardiac dipole eccentricity, horizontal QRS forces may appear upward directed (Gardberg, 1954). Finally, using the " cube " lead system the vertical component of the cardiac force is augmented whilst the transverse and sagittal components are foreshortened (Frank and Kay, 1955). This results in augmentation of upward directed cardiac forces.

In the vertical lead, normal downward orientation of QRS forces causes a predominantly negative QRS complex (Fig. 1). When QRS forces are upward directed the vertical lead becomes predominantly positive. This happens occasionally in controls and, to a greater degree (as shown by the abnormal R/Q ratio and R voltages) in subjects with left ventricular hypertrophy (Fig. 2). Owing to leftward QRS force orientation in both normal and in the abnormal group, the

TABLE I

Findings not encountered in 119 normal subjects, and the incidence of these findings in 42 subjects with left ventricular hypertrophy. R*t*, transverse lead R wave; S*s*, sagittal lead S wave; R*v*, vertical lead R wave.

	No. of cases
Vertical lead:	
R wave greater than 0·4 mV	5
R/Q ratio 3 or more	8
S–T segment elevation greater than 0·05 mV	4
T wave diphasic	7
T wave isoelectric, with QRS voltage greater than 0·5 mV	2
Transverse lead:	
S–T segment depression by 0·05 mV or more	21
T wave diphasic	5
T wave isoelectric	3
T wave negative	12
Sagittal lead:	
QS configuration of the QRS complex	2
S wave greater than 0·45 mV	8
S/R ratio greater than 6	12
Composite voltages:	
R*t* + S*s* greater than 1·5 mV	2
R*v* + R*t* greater than 1·3 mV	5
Total showing ST,T changes	26
Total showing QRS changes	18
Total showing ST,T or QRS changes or both	34

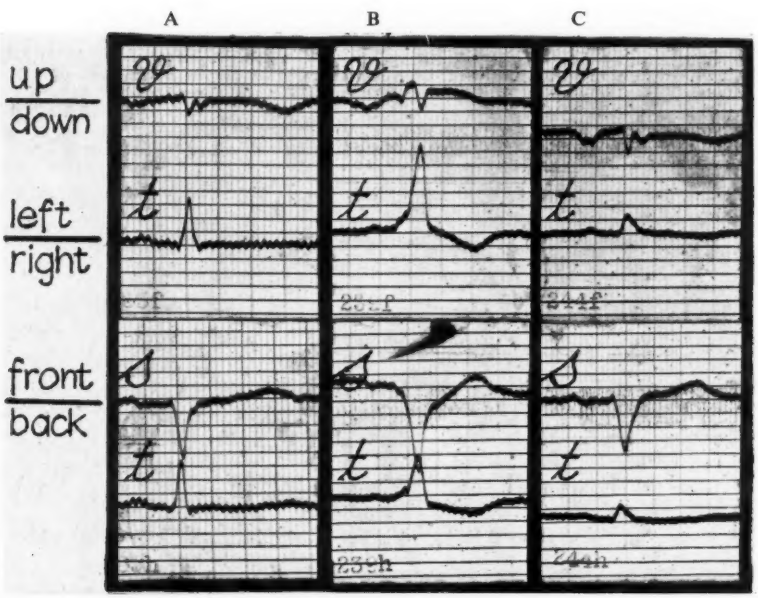


FIG. 5.—*Bizarre vertical lead QRS*, as seen in 3 subjects of the LVH, and in none of the normal, group. Abnormal isoelectric T wave in the transverse lead of record A, abnormal inverted transverse lead T wave in records B and C, abnormal elevated vertical lead S–T segment in record B. Abbreviations as in Fig. 1.

transverse lead displays a prominent R wave. In the sagittal lead, the backward orientation of forces in LVH causes a mainly negative QRS complex (Fig. 3). Such a QRS complex was also found in some normal subjects, but without the abnormal S/R ratio and S voltages seen in LVH. It is difficult to explain the bizarre QRS complex in the vertical leads of three of the abnormal group (Fig. 5). Incomplete left bundle-branch block is a possibility, particularly in Fig. 5B and C; since in the former QRS duration is 0·11 sec. and, as shown by the positive QRS onset, the initial forces are leftward directed in both records.

Of all the calculated quantities within the QRS complex the R/Q ratio in the vertical, and the S/R ratio in the sagittal lead were the most useful. That ratios of opposing forces may prove a useful substitute for lead voltage and vector magnitude measurement, and a temporary short-cut to the solution of the lead problem until more accurate leads than those now in use are found is suggested by the following. The voltage in a lead is, owing to body non-homogeneity and surface configuration and to eccentricity of the cardiac dipole, not a simple geometric projection of the dipole on the lead axis, but a scalar product of that projection and the lead vector of Burger and van Milaan (1948). Since the lead vector varies from lead to lead and is unknown in the living subject, absolute voltages in leads are devoid of quantitative meaning in relation to the cardiac dipole force. On the other hand and there is no evidence to the contrary, if the lead vector were constant throughout QRS, any ratio of two voltages within one QRS complex would contain the same lead vector in both denominator and numerator. The ratio is therefore independent of the lead vector and consequently of the inaccuracies of which this vector is a collective expression.

In left ventricular hypertrophy the R wave in leads aVL, V5, and V6 may show abnormally high voltage. In the present abnormal group of 42 subjects R in lead aVL was 11 mm. or greater in sixteen instances; RV5 or RV6 26 mm. or more in four instances (Sokolow and Lyon, 1949); aVL 13 mm. or more (Goldberger, 1949), in twelve instances. As leads aVL, V5, and V6 have approximately transverse lead axes, high voltage of the transverse lead of the " cube " lead system was also expected. In fact the transverse lead of the " cube " failed in this respect for the normal and abnormal voltages of the R wave in this lead overlap and it was not possible to define a normal maximum value. This observation is in keeping with the fact that past published work on the vectorcardiogram of left ventricular hypertrophy, employing the Duchosal-Grishman " cube " has not yielded a quantitative definition of QRS force magnitude in left ventricular hypertrophy. It is also to be expected from the fact that the axis of the transverse lead of the " cube " deviates clockwise from an ideal transverse lead (Frank, 1955; Schaffer, 1956) whereas the axis of lead aVL (and lead I) deviates counterclockwise. As LVH forces often point left and upward, they tend to parallel the axes of aVL and lead I and to lie perpendicularly to the transverse lead of the " cube." This could result in augmentation of these forces by the former leads and in attenuation by the latter lead. The opposite will apply to normal left and downward directed forces. Thus departing from an ideal transverse lead, leads I and aVL exaggerate, the transverse " cube " lead reduces the quantitative difference between normal and LVH forces. In addition the transverse lead of the " cube " foreshortens transverse cardiac forces (Frank, 1955), thereby acting as a short and relatively insensitive scale for their measurement.

The data on which the diagnosis of LVH was based in the present study, namely QRS configuration, voltage measurement, and S–T, T changes, would all be available had leads been recorded consecutively with a single-channel instrument. On the other hand, with regard to vectorcardiographic data, it was found that if consecutively recorded leads were aligned in a manner suggested by Goldberger (1953), the direction of vectors could be determined with reasonable accuracy but the direction of loop inscription was occasionally reversed by the procedure of alignment.

Summary

The three leads of the cube lead system and the conventional 12-lead electrocardiogram were recorded with a scalar electrocardiograph in 119 control and in 42 subjects with arterial hypertension or aortic regurgitation. The three leads of the cube were so connected that positive

deflections in the vertical lead meant upward, in the transverse lead leftward, and in the sagittal lead forward, directed cardiac forces.

The QRS complex of the vertical lead was negative (rS, rSr', Qr), owing to downward QRS forces, in 112 normal and 21 abnormal subjects. It was positive (qR), owing to upward directed forces, in 7 normal and in 16 abnormal subjects but qR configuration with a R/Q ratio of 3 or more and an R wave greater than 0·4 mV occurred only in the abnormal group.

Owing to leftward directed ventricular forces the QRS complex of the transverse lead was positive (qR, qRs, Rs) in all normal and abnormal records.

The QRS complex of the sagittal lead showed Rs or RS configuration in 99 normal and 14 abnormal subjects. Owing to backward directed forces, it was mainly negative (rS) in 20 normal and in 28 abnormal subjects but rS configuration with an S/R ratio greater than 6 and an S wave greater than 0·45 mV occurred only in the abnormal group. QS configuration in the sagittal lead, caused by totally backward QRS forces, was found only in two abnormal subjects.

$Rv+Rt$ exceeded 1·3 mV in five, and $Rt+Ss$ exceeded 1·5 mV in two subjects of the abnormal and in none of the normal group.

The QRS pattern and voltage changes enumerated, together with S–T/T changes described in the text, allowed the diagnosis of left ventricular hypertrophy in 34 of the 42 subjects in the abnormal group. The 12-lead electrocardiogram permitted this diagnosis in 33 to 37 subjects depending on the criteria for diagnosis of LVH which were used.

Conventional leads with near-transverse lead axes (lead I, aVL), distinguish between the normal and left ventricular hypertrophy in terms of QRS voltage. The transverse lead of the cube fails to do so.

The R/Q ratio in the vertical and the S/R ratio in the sagittal lead are more useful in the diagnosis of LVH from three orthogonal leads, than absolute QRS voltage measurements. Reasons are given for the view that ratios of forces within a single QRS complex are more independent of the error introduced by body characteristics and by dipole eccentricity than are absolute voltages.

The essential vectorcardiographic criteria of left ventricular hypertrophy may be recognized by inspection of the three leads.

It is a pleasure to acknowledge the valuable technical assistance of Mr. A. Fischman and Miss Marlene Watson.

References

Burger, H. C., and van Milaan, J. B. (1948). *Brit. Heart J.*, **10**, 229.
Duchosal, P. W., and Sulzer, R. (1949). *La Vectorcardiographie*. Bale.
Fischmann, E. J., and Brown, D. (1954). *Brit. Heart J.*, **16**, 351.
—— E. J. (1955). *Brit. Heart J.*, **17**, 496.
Frank, E., Kay, C. F., Seiden, G. E., and Keisman, R. A. (1955). *Circulation*, **12**, 406.
—— and Kay, C. F. (1955). *Amer. Heart J.*, **49**, 670.
Gardberg, M. (1954). *Circulation*, **10**, 544.
Gardiner, J. M., and Lowe, T. E. (1953). *Australasian Ann. Med.*, **2**, 22.
Goldberger, E. (1949). *Unipolar Lead Electrocardiography*. 2nd ed., Philadelphia.
—— (1953). *Unipolar Lead Electrocardiography and Vectorcardiography*. Philadelphia.
Horan, L. G., Burch, G. E., Abildskov, J. A., and Cronvich, J. A. (1954). *Circulation*, **10**, 728.
Newman, V. E., McGovern, J. F., and Arnold, T. G. (1955). *Arch. intern. Med.*, **96**, 591.
Portheine, H. (1955). *Zeitschr. Kreislaufforschg.*, **44**, 368.
Schaffer, A. I. (1956). *Amer. Heart J.*, **51**, 588.
Scherlis, L., Grishman, A., Sandberg, A. A., and Dvorkin, J. (1951). *Amer. Heart J.*, **41**, 494.
Schmitt, O. K., and Simonson, E. (1955). *Arch. intern. Med.*, **96**, 574.
Shillingford, J., and Brigden, W. (1951). *Brit. Heart J.*, **13**, 233.
Sokolow, M., and Lyon, T. P. (1949). *Amer. Heart J.*, **37**, 161.
Wenger, R. (1956). *Klinische Vektorkardiographie*. Darmstadt.
Wolff, L. (1955). *Dis. Chest*, **27**, 263.
——, Richman, J. L., and Soffe, A. M. (1953). *New England J. Med.*, **246**, 810 and 851.

THE SPATIAL VECTORCARDIOGRAM IN HYPOTHERMIA

BY

D. EMSLIE-SMITH*

From the Baker Medical Research Institute, and Clinical Research Unit, Alfred Hospital, Melbourne, Australia

Received August 8, 1957

In hypothermia characteristic changes appear in the electrocardiogram of man and other animals. Most striking of these is a slowly inscribed deflection that appears at the junction of the QRS complex and the S–T segment and grows in amplitude and duration as temperature falls (Emslie-Smith, 1956) (Fig. 1). This deflection, which was first described by Grosse-Brockhoff and Schoedel (1943), is not usually seen in all leads. In man some leads may show, instead, a widening of the base of the QRS complex.

In order to investigate the nature of this deflection more fully, spatial vectorcardiogram loops have been constructed for five patients and one dog, before and after cooling. Hypothermia produces consistent changes in the spatial vectorcardiogram unlike any previously described.

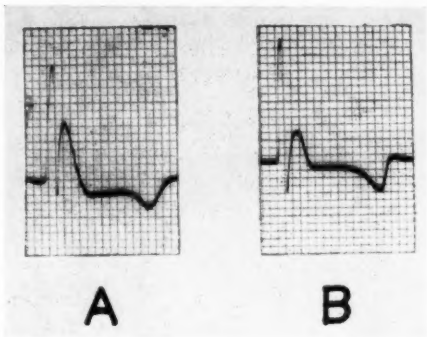


FIG. 1.—(A) Præcordial lead V4 recorded from a man with a normal heart at a temperature of 32° C. (rectal). (B) Direct electrogram recorded from the epicardium of the left ventricle of a dog at a temperature of 25·2° C. (œsophageal).

MATERIAL AND METHODS

Each of the five patients had suffered recent subarachnoid hæmorrhage from a congenital cerebral aneurysm. There were four women and one man, their ages ranging from 27 to 49 years. Hypothermia in preparation for craniotomy was produced by the technique of skin-cooling previously described (Emslie-Smith, 1956). Rectal temperatures were recorded by a thermistor apparatus. One patient (Case 3) had mild diastolic hypertension at the time of observation, but no clinical or electrocardiographic evidence of heart disease.

After the patients were anæsthetized, but before they were cooled, the electrocardiogram was recorded on a direct-writing electrocardiograph (Electrite, Cambridge Instrument Co. Ltd.) using standard and unipolar limb leads, and præcordial leads V1 and V4. It was again recorded after cooling. After complete

* Edward Wilson Memorial Fellow, 1955–56. Present address: Dept. of Medicine, Queen's College, Dundee.

recovery from the operation simultaneous records of leads aVR and aVL, V1, and V4 (and sometimes also of V4 and aVL) were made at fast paper-speed on a photographically-recording, mirror-galvanometer electrocardiograph (New Electronic Products Ltd.). At this time direct three-plane vectorcardiograms were also recorded by the method of electronic synthesis described by Lowe and Goble (1952). The projections of the vectorcardiograms in the three planes were those recommended by the American Heart Association (Wilson *et al.*, 1954).

From leads aVR, aVL, V1, and V4 frontal and horizontal vectorcardiograms were graphically derived, using the conventions employed by Lowe and Goble (1952). These were combined, as plan and elevation, to make three-dimensional wire models of the QRS and T spatial vectorcardiogram loops before and after cooling.

The dog was anæsthetized with intravenous pentobarbitone and the temperature was reduced by skin cooling. Electronic three-plane vectorcardiograms were recorded before and during cooling, using a modification of the cuboidal electrode placement of Duchosal and Sulzer (1949). From the records thus obtained three-dimensional wire models were constructed to show the spatial vectorcardiogram before and after cooling.

From the wire models the angles of the axes of the QRS and T loops, and the spatial angle between these axes (QRS–T spatial angle), were measured and recorded according to the conventions of Lowe and Goble (1952).

Results

In most cases the frontal and horizontal vectorcardiograms (VC) that were graphically derived from scalar leads before cooling resembled fairly closely those obtained by electronic synthesis at normal temperatures after operation. There were sometimes minor differences in the orientation of loops of similar shape (Fig. 5).

At normal temperatures 4 out of 5 of the human vectorcardiograms were within normal limits, and in Case 3 it was suggestive of mild left ventricular hypertrophy, although in the scalar leads the only abnormality was slight flattening of T in aVL.

Before cooling, the QRS vector loop from the dog was directed more anteriorly than would be normal in man but in other respects it closely resembled a human vectorcardiogram with a QRS loop of semivertical type (Fig. 2 and 3).

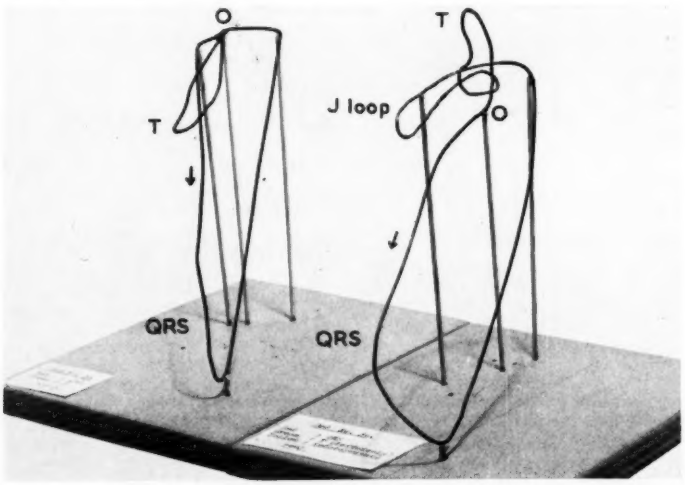


FIG. 2.—Wire models of the electronically synthesized spatial vectorcardiogram loops of dog at œsophageal temperatures of 37° C. (left) and 29° C. (right). The P loop is not shown. The loops are viewed from the front, slightly above and to the (model's) left of the origin (O). The arrows denote the direction of inscription of the QRS loops. Note the extra J loop characteristic of hypothermia.

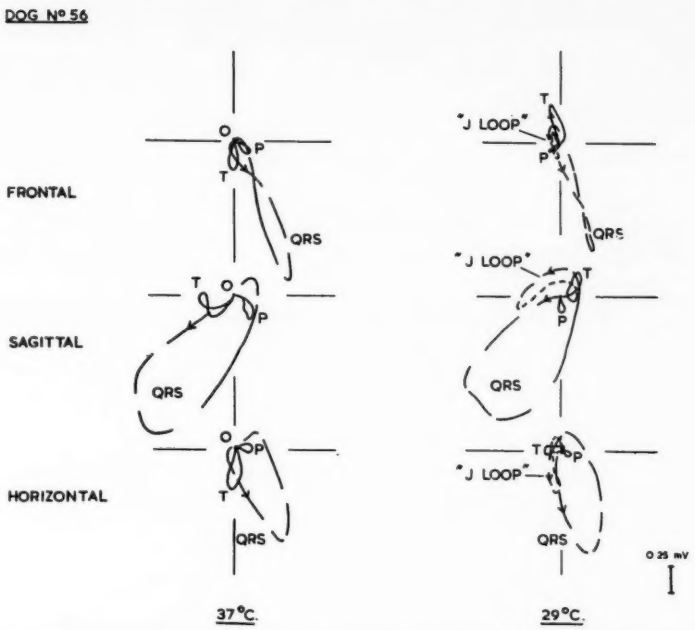


FIG. 3.—The vectorcardiographic loops in three planes (traced from the photographic records) from which the wire models in Fig. 2 were constructed. The inscription of the loops is interrupted, by a blanking pulse, every 0·006 sec.

Striking and consistent changes appeared in the vectorcardiograms of all five patients on cooling to 31·5° C. or lower. The main part of the QRS loop was essentially unchanged, but deformity appeared in each case in the terminal crochet of the QRS loop and in the junction (J) of the QRS and T loops, and sometimes in the T loop.

An extra loop appeared between the QRS and T loops, directed forward and to the left in all cases, and also downward in four. In all cases it was inscribed clockwise in the horizontal plane (Fig. 4), and in four cases it involved a J-shift, the QRS loop failing to return to the origin (O). For this reason it may be referred to as the J loop. It was larger than the T loop in two cases (Cases 1 and 4) and in Case 1 its total length in the horizontal plane was little smaller than that of the QRS loop (Fig. 4). The rate of inscription of the J loop was much slower than that of the QRS loop, and it slowed progressively during the course of each inscription, so that it finally approached that of the T loop (Fig. 3). The T loop that followed this extra loop was open, and in Cases 1 and 5 the QRS–T spatial angle was increased.

After cooling the dog to 29° C. the direct, electronically synthesized vectorcardiogram showed the same features as those of the human subjects, but the J loop was directed forward, slightly down, and slightly to the right. The QRS–T spatial angle was greatly increased, the T loop pointing in a direction almost opposite to its original one (Fig. 2 and 3).

Detailed descriptions of the spatial vectorcardiogram loops of the dog and of one human patient are given below. Details of the J loops and changes in QRS–T spatial angle seen in hypothermia in all five patients, and in the dog, are shown in Table I.

DETAILS OF CASE 4

Normal Temperature (37·4° C.). The QRS loop is inscribed clockwise in the frontal plane, and anticlockwise in both sagittal and horizontal planes. It is wide and semivertical. The initial crochet runs up

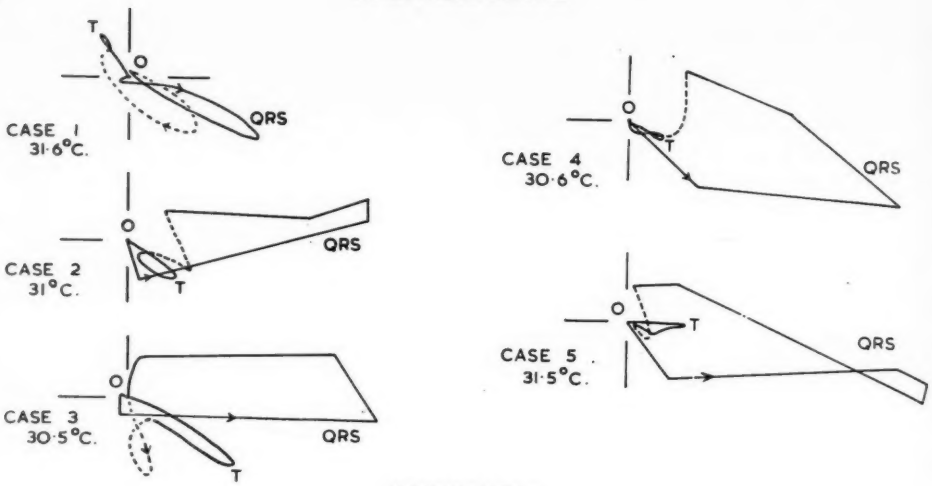


FIG. 4.—Graphically-derived vectorcardiographic loops in the horizontal plane of all five patients at low temperature. The J loop is shown as dotted, and is inscribed in a clockwise direction in all cases.

TABLE I

DETAILS OF J LOOPS AND CHANGES IN QRS–T SPATIAL ANGLES ON COOLING

Case No.	Rectal temperature (° C.)	J loop			QRS–T spatial angle
		Shape	Direction of inscription in space		
			Centrifugal limb	Centripetal limb	
1	Normal				18°
	31·5	Oval Very large	D, F, L*	U, B, R	130°
2	Normal				25°
	31·0	V-shaped	D, F, l	U, F, R	25°
3	Normal				50°
	30·5	J-shaped	d, F, L	U, B, r; then B, D	35°
4	Normal				25°
	30·6	V-shaped	D, F, l	U, b, r	15°
5	Normal				25°
	31·5	J-shaped	U, F, l	D, B, R	40°
Dog	Normal				25°
	29·0	See Fig. 2	d, F, R	u, B, r; then curls to L and R	150°

* D=down, U=up; F=forward, B= back; L=to the left, R=to the right. Small letters imply only a small change in direction, e.g. d=slightly down.

slightly to the right and slightly back. The centrifugal limb runs to the left, slightly down and slightly forward, then it turns steeply down, slightly forward and slightly to the left. The centripetal limb runs back, up and to the right, then turns forward, up and to the right, to O. The QRS axis angles are 60° in the frontal, 110° in the sagittal, and 20° in the horizontal plane. The T loop is oval, with its apex slightly below, to the left, and in front of O. Its axis angles are 35° in the frontal, 125° in the sagittal, and 25° in the horizontal, plane. The QRS–T spatial angle is 25°. This is a normal, derived VC (Fig. 5 and 6).

After Cooling (30·6° C.). The QRS loop of the derived vectorcardiogram is inscribed clockwise in the frontal, and anticlockwise in the sagittal and in the horizontal, plane. The initial crochet runs up and slightly to the right. The centrifugal limb runs to the left and slightly forward, turns steeply down to the left and slightly forward, and then curves back and slightly to the right. The centripetal limb runs down and back to the right; then it turns sharply up to the right and slightly back, to a point to the left of O, where the J loop begins. The QRS axis angles are 50° in the frontal, 100° in the sagittal, and 20° in the horizontal plane. The J loop is V-shaped. Its centrifugal limb runs down, forward, and slightly to the left; its centripetal limb runs up, slightly back and to the right, to a point slightly above, to the right, and slightly in front of O, where the T loop begins. The open T loop is narrow and twisted, with its apex below, to the left and in front of O. Its axis angles are 30° in the frontal, 140° in the sagittal and 30° in the horizontal, plane. The QRS–T spatial angle is 15° (Fig. 5 and 6).

Details of a Dog

Normal Temperature (37° C.). The electronically synthesized QRS loop is inscribed in a figure of eight in the frontal plane, and anticlockwise in both sagittal and horizontal planes. Its position is semivertical. The initial crochet runs forward, to the right and slightly down. The centrifugal limb runs to the left,

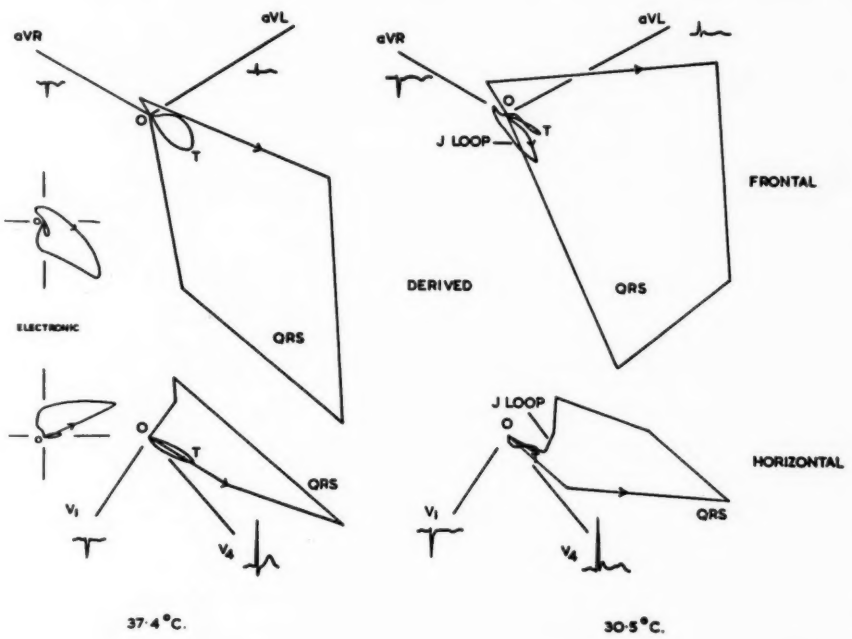


FIG. 5.—Frontal and horizontal QRS and T loops at 37·4° and 30·5° C. in Case 4. The large vectorcardiograms were graphically derived from the scalar lead complexes shown. The small ones were electronically recorded at normal temperature. Apart from a difference in orientation in the horizontal plane the graphic and electronic loops resemble one another. At 30·5° C. the J loop has appeared.

down and forward; the centripetal limb runs up, back and to the right, to a point behind and to the left of O, then in to O. The QRS axis angles are 65° in the frontal, 125° in the sagittal, and 55° in the horizontal plane. The T loop is narrow, directed forward and down from O. Its axis angles are 90° in the frontal, 140° in the sagittal, and 85° in the horizontal plane. The QRS–T spatial angle is 25°. Judged by human criteria the QRS and T axis angles are too large in the horizontal, and the T axis angle too large in the sagittal, plane: that is, the QRS loop is directed too anteriorly. Apart from this the vectorcardiogram resembles that from a normal man (Fig. 2 and 3).

After Cooling (29° C.). The electronically synthesized QRS loop is inscribed in a figure of eight in the frontal plane, and anticlockwise in the sagittal and horizontal planes. Its position is unchanged. The initial crochet is absent, the centrifugal limb running forward to the left and down. The centripetal limb runs up and almost straight back to a point behind, slightly above and slightly to the left of O, where the J loop begins. The QRS axis angles are 65° in the frontal, 135° in the sagittal, and 75° in the horizontal plane. The J loop is conspicuous. Its centrifugal limb runs forward, to the right and slightly down. Its centripetal limb runs back, slightly up and slightly to the right; then it curls down to the left, and up again to the right to start the T loop. The T loop is U-shaped. Its centrifugal limb runs up, slightly to the right and slightly back; its centripetal limb runs down, slightly to the left and forward to O. The T axis angles are −110° in the frontal, 70° in the sagittal and −140° in the horizontal, plane. The QRS–T spatial angle has increased to 150° (Fig. 2 and 3).

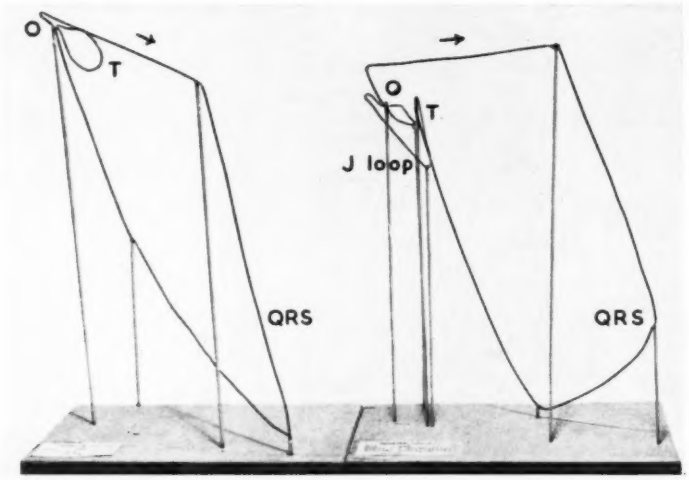


FIG. 6.—Wire models of the spatial vectorcardiographic loops (QRS and T) of Case 4 at 37·4° C. (left) and 30·5° C. (right). The loops are viewed from the front and slightly above. Arrows denote the direction of inscription of the QRS vector loops.

DISCUSSION

Vectorcardiograms derived from scalar leads by graphic methods are known to be considerably less accurate than those directly obtained by electronic synthesis (Sayers, 1952), particularly if the scalar tracings used for the construction of a loop in any one plane are not recorded simultaneously. In this study it was impossible to use the bulky and relatively fixed vectorcardiograph apparatus in the neurosurgical operating theatre, and non-simultaneous directly-written scalar tracings had to be used. However, by later recording the relevant scalar tracings simultaneously on a photographically-recording electrocardiograph, simultaneous points of reference could be identified on each of the paired tracings recorded in the theatre. In this manner errors due to phase-shift should be largely eliminated. As a further check the frontal and horizontal vectorcardiograms

thus graphically derived at normal temperatures were compared with those later recorded directly from the same patient by electronic synthesis. These precautions suggest that apart from some discrepancies of orientation, perhaps due to posture and the effects of anæsthesia, the derived vectorcardiograms probably resemble those that would have been obtained electronically. This belief is strengthened by the fact that the vectorcardiogram of the dog, recorded directly by electronic means throughout cooling, showed essentially the same change as the loops graphically derived from the patients.

This appears to be the first study of the effect of hypothermia on the vectorcardiogram. It demonstrates that cooling produces gross consistent changes in the spatial vectorcardiogram of man and dog. The characteristic change during hypothermia is a disturbance involving the terminal crochet of the QRS loop, the junction (J) of the QRS and T loops, and the T loop. The last part of the centripetal limb of the QRS loop is suddenly deflected forward and greatly slowed, so that the QRS loop does not always return to the point of origin (J-shift) but continues, to form an extra, conspicuous open loop. This, in turn, continues into a more or less U-shaped T loop which may lie in a direction different from that seen at normal temperature (Fig. 2).

This striking J loop is unlike anything seen in left or right bundle-branch block (Lowe and Gardiner, 1954) or ventricular hypertrophy (Gardiner and Lowe, 1953 and 1954). Spatially it appears to begin before the QRS loop is ended, but in rate of inscription it more resembles the T loop, with which it is directly continuous. In some cases as cooling proceeds there is a progressive increase in the QRS–T spatial angle, and at low temperatures the long axis of the T loop may lie almost opposite in direction to the QRS loop. When this occurs the J and T loops may form a more or less continuous loop as large as the QRS loop. The fact that changes also appear in the T loop does not necessarily imply that they are causally related to the development of the J loop, for both changes might arise independently, from the effects of hypothermia.

From this study alone it is impossible to draw any conclusion about whether hypothermia primarily disturbs the process of depolarization or of repolarization, or both. The new J loop involves both the terminal crochet of the QRS loop and the first part of the T loop. Its rate of inscription progressively slows, to approach that of the T loop (Fig. 3). The work of Burgen and Terroux (1953) and of Coraboeuf and Weidmann (1954) has shown that cooling slows the processes of depolarization and repolarization of the single myocardial fibre at different rates. This implies that in the intact heart the overall relationship between the processes of depolarization and repolarization is altered in hypothermia. An alteration of this nature could be expected to modify the total unbalanced electrical activity of the heart during the part of the cycle when depolarization is normally ending and repolarization is beginning. This is precisely the part of the cycle occupied by the characteristic scalar deflection of hypothermia and the J loop of the vectorcardiogram. Since the electrocardiogram represents the total unbalanced electrical activity of the heart, manifest in terms of potential difference at the site of the electrode, the J loop of the vectorcardiogram and the characteristic deflection in scalar leads may reflect the altered relationship between depolarization and repolarization that is produced by hypothermia.

Summary

From scalar-lead electrocardiograms of five patients without heart disease, vectorcardiograms in the frontal and horizontal planes were graphically derived for normal and low temperatures. Wire models of the spatial vectorcardiograms were constructed.

In hypothermia the main part of the QRS loop was essentially unchanged but below 31·5° C. consistent alterations appeared in the terminal crochet of the QRS loop, in the junction (J) of QRS and T loops, and in the T loop. An extra loop (J loop) appeared between the QRS and T loops, inscribed clockwise in the horizontal plane and directed forward, to the left, and usually downward. Its rate of inscription slowed progressively during the course of each inscription, so that finally it approached that of the T loop. The spatial angle between the QRS and T loop sometimes increased greatly.

Three-plane electronic vectorcardiograms were made during the cooling of one dog. The spatial vectorcardiogram at 29° C. showed an increase in the QRS–T angle and a J loop similar to those derived from the human subjects.

The J loop may represent an altered relationship between the overall processes of depolarization and repolarization in hypothermia.

I should like to thank Mr. K. C. Bradley and Dr. R. H. Orton for permission to study and report these cases, Dr. T. E. Lowe (Director of the Baker Medical Research Institute and Alfred Hospital Clinical Research Unit) for his help and encouragement, and Professor I. G. W. Hill for his help in the preparation of the manuscript. I thank the Editor, *Australasian Annals of Medicine*, for permission to reproduce Fig. 1.

REFERENCES

Burgen, A. S. V., and Terroux, K. G. (1953). *J. Physiol.*, **119**, 139.
Coraboeuf, E., and Weidmann, S. (1954). *Helv. physiol. pharmacol. Acta.*, **12**, 32.
Duchosal, P. W., and Sulzer, R. (1949). *La Vectocardiographie*. Basle, S. Karger.
Emslie-Smith, D. (1956). *Aust. Ann. Med.*, **5**, 62.
Gardiner, J. M., and Lowe, T. E. (1953). *Aust. Ann. Med.*, **2**, 22.
——, —— (1954). *Aust. Ann. Med.*, **3**, 18.
Grosse-Brockhoff, F., and Schoedel, W. (1943). *Arch. Exper. Path. Pharmakol.*, **201**, 417.
Lowe, T. E., and Goble, A. J. (1952). *Med. J. Aust.*, **1**, 503.
——, and Gardiner, J. M. (1954). *Aust. Ann. Med.*, **3**, 289.
Sayers, B. McA. (1952). *Aust. Ann. Med.*, **1**, 154.
Wilson, F. N., Kossmann, C. E., Burch, G. F., Goldberger, E., Graybiel, A., Hecht, H. H., Johnston, F. D., Lepeschkin, E., and Myers, G. B. (1954). *Circulation*, **10**, 564.

ANTI-STREPTOLYSIN O TITRE IN RHEUMATIC CARDITIS

BY

E. N. CHAMBERLAIN, C. A. ST. HILL, AND S. COPE

From the Royal Southern Hospital, Liverpool

Received August 28, 1957

The definition of rheumatic fever has been broadened of recent years and many people take it to include not only articular and skin manifestations but also all those signs that are commonly regarded as evidence of an active carditis. While this conception may be pathologically correct and at times convenient in use, it is clear that there are many cases of rheumatic fever where there is no proof of cardiac involvement and equally others where rheumatic involvement of the heart is evident without the other features of the rheumatic state.

The commonly held view that rheumatic fever is the sequel of a streptococcal infection led to the investigation of immune bodies produced by these streptococci amongst which are to be numbered the anti-streptolysins, anti-fibrolysin, and anti-hyaluronidase. In spite of modern diagnostic aids, recognition of the presence of rheumatic activity, especially in the heart, remains a problem of great difficulty. It seemed to us, therefore, that it was important to re-assess the various criteria by which rheumatism and rheumatic carditis are at present judged. Although most of our observations have embraced clinical, electrocardiographic, radiological, biochemical, and bacteriological investigations, the present report is devoted to the anti-streptolysin O titre (A.S.O.).

Our series differs from those of most hitherto published work in the length of observations made in the individual patient. The clinical and certain other observations have continued over several years. The anti-streptolysin studies extend over a period of many months and sometimes more than a year. Estimations were made fortnightly with an average of 12 for each patient.

Among previous studies of the anti-streptolysin O titre there is considerable variation in what should be accepted as normal. Rantz *et al.* (1952) gave figures of 150 for children between the ages of five and seven, and of 184 for those between eight and twelve. Faver (1953) regarded the level as normal below 200 and thought that when there was a rise above this level it was due to previous streptococcal infection. Denny *et al.* (1950) recorded a higher titre in those cases that developed rheumatic fever, while Rantz *et al.* (1948) found the titre lower in those who develop carditis than in those with joint pains. More recently Stollerman *et al.* (1956) accepted 200 as the upper limit of normal.

A great variation is also found in the type of the curve, which generally rose in one to two weeks and was maximal in four weeks (McCarty, 1952; and Bywaters, 1951). There was a conflict of opinion as to whether a rise always occurs when a patient develops rheumatic fever. Rantz *et al.* (1952), Bywaters (1951), McCarty (1952), and Todd (1932) suggest that this is so, but Chaptal *et al.* (1954), Faber (1953), Poppi (1952), Windblad *et al.* (1949), and Waksman (1949) deny it.

An opinion has been expressed partly on the basis of the anti-streptolysin O titre that rheumatic fever is streptococcal in origin. This view is held by Long (1954), Faber, Poppi, Bywaters, and Denny *et al.* (1950) but not by Waksman. The only specific references to the relationship of this titre to chorea since 1946 are by Poppi (1952) and Taranta and Stollerman (1956). In many of these papers a study of the erythrocyte sedimentation rate (E.S.R.) was made concurrently with the A.S.O., and Windblad *et al.* (1949) find the curves to be parallel.

Source of Material. Most of our observations were made upon children in St. Joseph's Heart Hospital, Rainhill, where children ranging in age from five to eighteen years continue their medical supervision and education often for several years. It gave us an unusual opportunity, therefore, of watching the development of cases of rheumatic carditis and noting the fluctuations in the disease from year to year. Most children are admitted to the hospital some time after the acute rheumatic process has subsided, but there is often information from other hospitals about the findings when the children were under their care. Some children were admitted when there was still doubt as to whether the carditis had completely settled and some developed further episodes of the rheumatic state or of carditis while they were in St. Joseph's.

When it was deemed justifiable each child was brought to the Royal Southern Hospital for a comprehensive clinical, electrocardiographic and radiological review. The blood specimens for the anti-streptolysin O titre and throat swabs were also brought to the Pathology Department of this hospital.

There were generally about forty children at St. Joseph's, but a few of these had congenital heart disease and only served as controls. The number of rheumatic cases was, however, increased by the addition of some admitted directly to the Royal Southern Hospital and to the Liverpool Regional Cardiac Centre, though generally these children were older. Later in the investigations one of us (S.C.) was able to add observations on children in Alder Hey hospital. In all 72 cases were investigated.

In view of the distance between the Convalescent Heart Hospital, St. Joseph's and the central hospitals in the city, it was not always possible to synchronize the investigations as we would have wished. The regular estimation of the anti-streptolysin O titres was, however, paralleled by an estimation of the E.S.R. and by throat swabs. Electrocardiograms were also available at regular intervals, and the clinical observations on the rheumatic and cardiac signs were made by two of us (E.N.C. and S.C.) in conjunction with Dr. D. M. Freeman, so that each child was generally seen at least once a week and more frequently in the event of a change in the condition. We were thus able in general to chart the variations of the A.S.O. titre against rheumatic signs, such as articular rheumatism and nodules, against fever, whether of rheumatic or non-rheumatic origin, and against the presence of active carditis. The technique for estimation of the A.S.O. titre was that described by Rantz and Randall (1945) using streptolysin O produced by the Wellcome Research Laboratories.

Results

Quiescent Cases (*Table I*). In many cases the level of the anti-streptolysin O titre was as low as 12 and quite often 50: these figures would by any standards be accepted as normal. There was, however, a considerable number with a titre ranging from 150 to 250, in which it was difficult to show any parallelism between this and any manifestation of the rheumatic state.

The 18 controls included two cases that had a history of rheumatic fever, two years previously in one and six months previously in the other, but no heart lesion; in these the anti-streptolysin O titre levels ranged from 100 to 250. In eight other cases of established valvular heart disease in whom no evidence of recent rheumatic activity or of streptococcal infection had been recorded (from periods varying from four months to nine years) the titres were generally below 180, occasionally up to 250 and in two cases (M.H. and J.F.) up to 350. The reason for levels above the accepted normal was obscure, though there may have been a cryptic streptococcal infection, but it emphasizes the importance of admitting a large variation in titre as having no relationship either to rheumatic fever or rheumatic carditis. The remaining controls were provided by following the titres of eight children with congenital heart disease (not shown in the Table). In these cases likewise a variation of the titre from levels of 12 to 250 was noted.

With these figures as a basis it appeared that the best way of assessing the significance of any rise in titre in relation to rheumatic carditis was to determine whether any patterns exist and compare them with the pattern in caditis. We have attempted to do this in relationship to: (1) controls,

(2) rheumatic fever, (3) chorea, (4) rheumatic carditis, (5) fever not attributable to the rheumatic state, and (6) congestive cardiac failure.

Rheumatic Fever (*Table II*). This term has been used here to denote the fifteen cases of fever accompanied principally by articular manifestations but also by rheumatic nodules or rashes. It was in those with joint manifestations that the highest figures for the A.S.O. titre (500–1250) were found. In several instances when the clinical course of the illness was short, even though the attack was sharp, there was an early rise and rapid fall in the A.S.O. titre roughly corresponding with the clinical pattern.

In our small series no significant difference was observed between the figures in the first or subsequent attacks of rheumatic fever. The mean level of the rise and fall of the anti-streptolysin O titre is seen in the Figure, but there are considerable variations, more apparent in the Tables. In the three cases with only minor rheumatic manifestations, the A.S.O. titre figures were

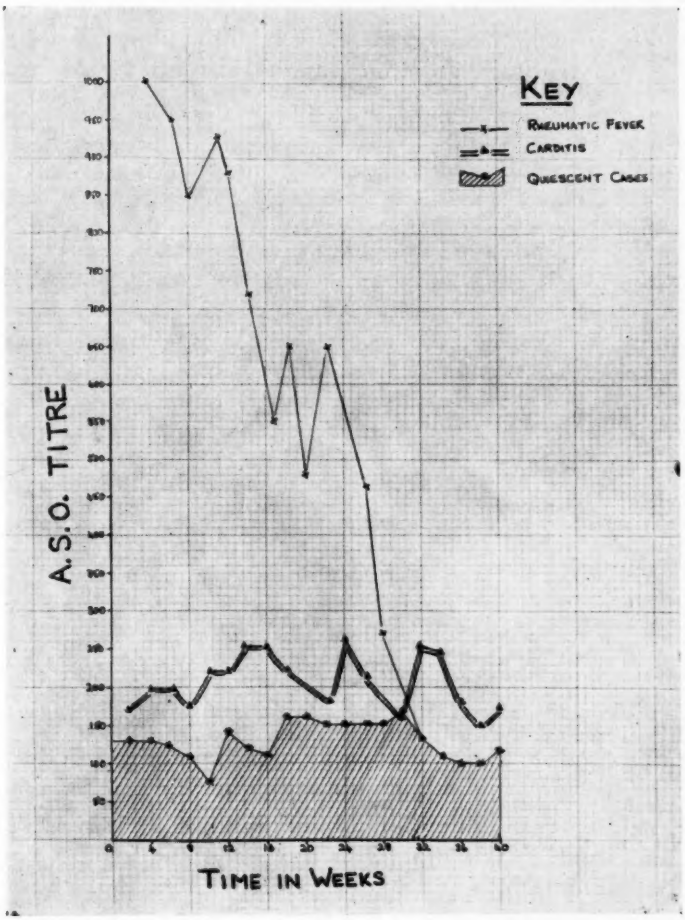


FIG. 1.—Mean rate of fall of anti-streptolysin O titre in cases of rheumatic fever compared with those with rheumatic carditis and quiescent cases.

TABLE I
QUIESCENT CASES

Name	Titre during 26 weeks of the observation period												
	0–2	2–4	4–6	6–8	8–10	10–12	12–14	14–16	16–18	18–20	20–22	22–24	24–26
* D. C.	250		250		180	250	100	180	250		180		
* J. L.	250	180	180	125	125	180	250	125					
J. McD.	180		180	125	50	180	125	50	180	250	250	100	180
M. H.	250	250	180	180	250	250	250	250	250	250	350	350	350
P. A.	12	12	12	12	12	12	12	12	12	12	12	12	12
J. F.	180	125	250	100	50	180	100	180	350	180	125	350	180
G. W.	180	180	50	50	12	180	50	50	125	125	100	50	12
M. H.	250	250	250	180	125	125	180	180	250	250	250	250	180
J. H.	50		100			50	50	12	12	50	12	50	50
B. O'C.	180	180	50	50	12	180	100	50	125	125	180	100	125

* All patients had valvular disease of the heart except these two who had no organic disease.

TABLE II
CASES OF UNCOMPLICATED RHEUMATIC FEVER

Name	Weeks after onset of disease												
	2–4	4–6	6–8	8–10	10–12	12–14	14–16	16–18	18–20	20–22	22–24	24–28	28–30
Y. L. K.	1250	500	900	350								180	
K. M.						125	100	100	50	50	50	50	50
A. I.			620	900		1250	1250	1250	1250	1250	1250	900	500
M. McG.		900	900	500	250		620	620		500			
G. B.	125	350	1250										
P. M.	1250		1250		1250								
C. Sa.		1250	1250	1250	1250	1250							
A. H.	1250	900	500	1250	1250	1250							
D. O.	1250	1250	900	1250									
J. St.			900	500	350	900	900						
A. G.	1250	1250	1250	500									
J. Ba.		1250	1250	900		500		250		125			
M. A.	1250	1250		900	900	900							
M. As.	1250	1250	900	900	900								
J. H.	1250	1250	900	900	1250								

comparatively low. The presence or absence of carditis did not appear to modify the A.S.O. pattern.

Chorea (*Table III*). Only twelve cases of chorea came under observation, a number inadequate to justify any firm conclusions. Our figures, however, support the observations of Poppi (1952) and Taranta and Stollerman (1956) who found that titres may be normal in chorea. They were normal in 5 of our cases, though in the remaining 7 they reached the level found in articular rheumatic fever. In cases where the titre was raised this might occur early or late in the disease. In this observation our results differed somewhat from those of Taranta and Stollerman who considered that the immunological responses in chorea may be declining as the disease appears: they claim that often the disease makes its appearance several months after other rheumatic manifestations. Table III shows the wide variation in patterns that may occur in chorea.

TABLE III

CASES OF CHOREA (UNCOMPLICATED)

Name	Weeks after onset of disease										
	2–4	4–6	6–8	8–10	10–12	12–14	14–16	16–18	18–20	20–22	22–26
D. B.	250	180	125	180	125	125	125	180	125	180	350
G. N.		50	12	50	50	50	50	50	50	50	50
J. B.		500	620	900	1250						
J. K.	1250	900	620	620							
J. S.	1250	1250	1250	1250	900	900	500	500	350	620	620

Rheumatic Carditis (*Table IV*). This is the group of cases in which we had particularly hoped for information. So that a comparison can easily be made, Table IV sets out examples of the A.S.O. titre in carditis alone, in carditis with rheumatic fever, and in carditis with chorea. In all 25 cases have been scrutinized. In fourteen of these we felt justified in regarding the diagnosis as certain; of these, eleven had other manifestations of rheumatism. The cardiac signs accepted as evidence of

TABLE IV

CASES WITH CARDITIS

Name	Other rheumatic manifestation	Weeks after the onset of disease																				
		0–2	2–4	4–6	6–8	8–10	10–12	12–14	14–16	16–18	18–20	20–22	22–24	24–26	26–28	28–30	30–32	32–34	34–36	36–38	38–40
A. T.	Nil	varying from 180 to 250																			
B. H.	Nil					500	620	500	350	180	180	250	500	350	500	250	620	620	350	250	250
T. R.	Nil	250	250	180	100	50	100	180	100	50	125	180	250	250	125	125	125	125	125	100	180
M. N.	Nil	125		180	180	100	50	50	50	50	50	50	50	50	50	50	125	50	50	50	50
J. F.	Nil	125	250	250	180	250	125	350	350	350	350										
G. Th.	R.F.	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	12	50	50
J. B.	R.F.		350	620	900	900	620	900	350	250	350	250	250	250	620	350	250	250	350	250	250
C.P.M.	R.F.					500	500	350	350	350	350	250	250	350	250	350	250	250	250	250	250
G. T.	R.F.					1250	1250	900	620	350	250	350	180	180		250	250	250	250	180	180
J. B.	Ch.			1250	900	1250	900	900	900												

carditis included pericarditis, the appearance of new and significant murmurs (especially an aortic diastolic or a Carey Coombs murmur), convincing electrocardiographic changes, and sometimes the precipitation of congestive cardiac failure without other evident cause. Those remaining were divided into four probable cases of carditis, of which one had rheumatic fever and one had chorea, and seven possible cases, of which four had rheumatic fever and one had chorea.

Except when there were associated signs of rheumatic fever, cases of carditis did not show very high titres. In one (G.Th.) even though there was an associated sore throat and joint pains the titre was low, but this was an unusual case and in most of the others the titre could be regarded as above normal. As will be related shortly, however, the figures were not greatly different from those observed when no rheumatic fever or carditis was present. Therefore it was impossible to correlate the level of the A.S.O. titre to the degree of carditis.

Sometimes the signs of carditis disappeared before the titre fell. This may of course merely indicate that the recognition of continuing carditis is impossible or, on the other hand, that the circulating antigen is being neutralized by increasing production of antibodies and is no longer free to provoke a response in the cardiac tissues. The interpretation is still largely a matter of speculation and will be discussed later.

Fever Not Attributable to the Rheumatic State (*Table V*). In 11 cases in which there was no evidence of rheumatic fever or active carditis but was fever that was attributed either to a respiratory infection or to some unknown cause, figures ranging from a low normal of 12 to a moderate rise of 350 were noted, as is shown in the five representative cases in Table V. It was difficult to identify the nature of the infection in these cases. It may have been viral in some instances or bacterial in others, and the possibility of some streptococcal invasion could scarcely be excluded by a clinical examination. This is an important group as it is always difficult in a child with recent rheumatism to interpret continued mild pyrexia and it is evident that a moderate rise in A.S.O. does not prove a rheumatic origin.

TABLE V

FEVERS THAT COULD NOT BE ATTRIBUTED TO THE RHEUMATIC STATE

Name	Causes of fever	Weeks after onset of disease									
		0–2	2–4	4–6	6–8	8–10	10–12	12–14	14–16	16–18	18–20
T. B.	Respiratory infection	125	180	100	125	250	180	350	180	250	180
D. G.	,, ,,	12	12		12		12		12		12
V. H.	,, ,,	180	350	180	250	125	250	250	250	250	350
B. B.	P.U.O.	250	180	50	12	12	12	50	12	12	50
P. M.	,,	180	250	180	250	125	180	250	250	250	250

Anti-streptolysin O Titre in Cardiac Failure. In view of the generally accepted opinion that the E.S.R. falls in congestive cardiac failure and therefore no longer represents the degree of activity in the rheumatic state, we thought it important to see whether the same held good for the anti-streptolysin O titre. Eight cases came under this heading, 5 precipitated by bronchitis and 3 by rheumatic carditis. In none of them did we observe any significant change in the titre because of the presence of cardiac failure.

Discussion

As a basis for the interpretation of the results set forth, we have accepted the current view that rheumatic fever, including rheumatic carditis, is attributable to an infection with Group A, β-hæmolytic streptococci (Pauli and Coburn, 1937; Todd, 1932; and others).

The complicated classification and sub-grouping of this streptococcus with the varying types of polysaccharides does not immediately concern us here, and of the soluble products emanating from the organism, our work bears only on A.S.O., which has been more widely studied than the S lysin owing to technical difficulties in the preparation and preservation of the latter.

We have accepted the general view that the variation of other anti-bodies, such as anti-fibrolysin, anti-streptokinase, and anti-hyaluronidase, runs roughly parallel with anti-streptolysin, though we realize that there are exceptions to this, and if it were practical it would be more accurate to have the levels of several antibodies estimated.

It was felt that a study of the anti-streptolysin O titre levels over a prolonged period might be of value in helping to assess the evidence of activity in carditis, an increasingly important diagnosis to make in studying the natural history of rheumatic valvular heart disease, with the eventual possibility of surgical treatment. Our results do not indicate that the anti-streptolysin values directly help towards this end, though they show that the highest figures are found in rheumatic fever with articular manifestations, agreeing with the observations of Denny *et al.* (1950). It is common knowledge that carditis may make its appearance during this active stage of articular rheumatism, i.e. at a time when the A.S.O. titre is raised. The presence of a normal titre might, therefore, reasonably be considered as against the presence of active carditis.

On the other hand, when non-cardiac manifestations of rheumatism were absent, the titre was never very high, even though the heart was clearly involved. This point was also made by Denny *et al.* (1950) and McCarty (1952). Yet although the titre was not very high in this group, it was rarely normal if a figure of over 200 is accepted as abnormal. Here again, therefore, the presence of a completely normal titre weighs against the diagnosis of active carditis.

The reason for a great rise of anti-streptolysin O titre in articular rheumatic fever with a much less significant rise in cases of carditis is obscure, as is the manner in which the streptococcus causes its effects. Our limited observations do not justify undue speculation in this wide field, but the possibility that a separate antigen-antibody reaction is responsible for the heart lesion might account for lower A.S.O. titre values than when the joints are affected.

This may mean that when articular rheumatism results from streptococcal infection the anti-streptolysin rises correspondingly, but that some further mechanism is then set in motion by which the heart may be damaged. If it is assumed that a factor A is responsible for articular and other non-cardiac rheumatism, and a factor B for the involvement of the heart, factor B might presumably work alone so that carditis could appear without other manifestations of rheumatism. Such a theory might also explain the occurrence of carditis in cases of chorea, but it remains, of course, for further research to show whether two or more factors are concerned and whether they must act synergistically or independently.

Summary

A study of the anti-streptolysin O titres over a prolonged period in children suffering from manifestations of the rheumatic state has been made. The upper limit of normal has been regarded as 200 units but occasional levels of 250 units were found in apparently healthy children.

The highest titre occurred in cases with joint manifestations. Cases with carditis alone did not show very high titres, though these were in general above normal limits.

Reference is made to the titre in other infections and congestive cardiac failure. The significance of these results is discussed.

We should like to thank the following for their invaluable assistance in their various fields: Dr. W. K. McGinley of Whiston Hospital, Liverpool, Professor N. B. Capon, Dr. R. W. Brookfield, and Dr. S. E. Keidan; also Dr. H. P. Tulloh, Sister V. Carroll, Mrs. A. Pemberton, and Miss D. Hunt of the Royal Southern Hospital, Liverpool; and finally Sister Mary Joseph and Sister Francis of the St. Joseph's Children's Heart Hospital, Rainhill.

We also acknowledge the grant, kindly made by the Board of Governors of the United Liverpool Hospitals, towards the laboratory expenses for this work.

References

Bywaters, E. G. L. (1951). *Brit. med. Bull.*, **8**, 346.
Chaptal, J., Jean, R., Campo, C., Alram, D., and Fraisee, J. (1954). *Arch. franç. Pédiat.*, **11**, 1055.
Denny, E. W., Wannamaker, L. W., and Rammelkamp, C. H. (1950). *Amer. J. Dis. Child.*, **80**, 506.
Faber, V. (1953). *Acta. med. scand.*, **147**, 299.
Long, D. A. (1954). *Lancet*, **1**, 529.
McCarty, M. (1952). *Arch. intern. Med.*, **37**, 1027.
Pauli, R. H., and Coburn, A. F. (1937). *J. exp. Med.*, **56**, 595.
Poppi, A. (1952). *Reumatismo*, **4**, 242.
Rantz, L. A., di. Caprio, J. M., and Randall, E. (1952). *Amer. J. med. Sci.*, **224**, 194.
—— and, Randall E. (1945). *Proc. Soc. exp. Biol., N.Y.*, **59**, 22.
—— —— and Rantz, H. H. (1948). *Amer. J. Med.*, **5**, 3.
Stollerman, G. H., Lewis, A. J., Schultz, I., and Taranta, A. (1956). *Amer. J. Med.*, **20**, 163.
Taranta, A., and Stollerman, G. H. (1956). *Amer. J. Med.*, **20**, 170.
Todd, E. W. (1932). *Brit. J. exp. Path.*, **12**, 248.
Waksman, B. H. (1949). *Medicine (Baltimore)*, **28**, 143.
Windblad, S., Magmross, H., and Wilander, O. (1949). *Acta. med. scand.*, **133**, 358.

THE INFLUENCE OF VENTRICULAR HYPERTROPHY UPON THE CARDIOGRAM OF ANTERIOR CARDIAC INFARCTION

BY

J. F. GOODWIN

Department of Medicine, Postgraduate Medical School of London

Received November 2, 1957

The presence of an S wave, preceded by an r wave in lead V5 (rS pattern) has been interpreted as indicating extreme clockwise rotation of the electrical position of the heart around its vertical axis (Goldberger, 1947, 1949). A deep S wave in V5 occurs in right ventricular hypertrophy (Myers *et al.*, 1948), while an R/S ratio less than unity in V5 (rS pattern) when occurring in conjunction with a qR pattern in VR, was considered by Pagnoni and Goodwin (1952) to be diagnostic of right ventricular hypertrophy in adults, in the absence of cardiac infarction, ventricular aneurysm, or right bundle-branch block. The rS pattern in V5 has also been shown to occur in combined ventricular hypertrophy (Goldberger, 1949; Pagnoni and Goodwin, 1952). A prominent S wave (not exceeding the R wave in amplitude) can occur in normal persons (Myers *et al.*, 1947). In Leatham's (1950) series of 100 normal subjects, the rS pattern occurred only in two, and R was equal to S in one other.

Although cardiograms have been published showing rS patterns in V5 in cases with autopsy proof of anterior infarction, (Myers *et al.*, 1949; Levy and Hyman, 1950) little has been written about this pattern in cardiac infarction.

The unexpected finding of anterior cardiac infarction at autopsy, in patients whose cardiograms showed no unusual features other than an rS complex in V5, prompted the present investigation into the genesis of this pattern, with special reference to right ventricular hypertrophy, combined ventricular hypertrophy, and cardiac infarction.

Case Material and Methods

Cardiograms were analysed from 85 adult patients with autopsy evidence of cardiac infarction, right ventricular, or combined ventricular, hypertrophy. Only cases showing a predominantly negative deflection in lead V5 were included but the study was not confined to rS patterns, cases with Qr and qrS patterns being also included.

Multiple-lead cardiograms were available, the leads examined being VR, VL, VF, and V1, V3, V5. In many cases lead V4R and leads V6 and V7 were also studied. Conventional standardization of 1 cm. = 1 mv. was employed.

Pathological Criteria

The criteria for ventricular hypertrophy previously reported by Pagnoni and Goodwin, 1952, and by Camerini *et al.* (1956), were employed, but no attempt was made to differentiate degrees of hypertrophy, since the presence of cardiac infarction in many cases rendered this impossible. Thickness of the outflow tract of the right ventricle of more than 5 mm. was considered to represent right ventricular hypertrophy, while thickness of the left ventricular muscle of more than 15 mm. was considered to represent left ventricular hypertrophy. Dilatation was also taken into account. All hearts had been examined for the presence and site of infarction.

Results

The cases were divided into six groups, according to the pathological findings, as follows.

Group	Necropsy findings	No. of cases
1	Lone right ventricular hypertrophy (RVH)	31
2	Right and left ventricular hypertrophy (R and LVH)	20
3	Infarction with lone right ventricular hypertrophy (RVH+I)	7
4	Infarction with lone left ventricular hypertrophy (LVH+I)	7
5	Infarction with combined ventricular hypertrophy (R and LVH+I)	12
6	Cardiac infarction without ventricular hypertrophy (I)	8
	Total	85

In Group 1, restriction to cases showing an rS pattern or a mainly negative wave in V5 eliminated many cases with autopsy and cardiographic evidence of right ventricular hypertrophy, while in Group 2, the same restriction resulted mainly in the inclusion of cases with greater hypertrophy of the right than of the left ventricle.

The site and other pathological data of the patients with infarction are shown in Table I.

TABLE I

Types of Myocardial Infarction in 34 Patients

Site of infarct	No. of cases	Other features
Anterior and septal	25	Involvement of posterior wall in 5. Cardiac rupture in 3 (2 septum, 1 anterior left ventricle). Cardiac aneurysm in 4
Pure anterior	4	—
Subendocardial	2	Cardiac rupture in 1
Posterior—small —large	1 2	Cardiac aneurysm in 1 —
Total	34	—

Cardiographic Analysis. In the analysis of all groups special attention was paid to the following points, having regard to the conventional criteria for right ventricular hypertrophy (Myers *et al.*, 1948; Camerini *et al.*, 1956), for combined hypertrophy (Pagnoni and Goodwin, 1952), and for cardiac infarction (Wilson *et al.*, 1944, 1947; Bain and Redfern, 1948):

Voltages of R and S waves in V4R, V1, V3, and V5.
R/S ratio in V4R, V1, V3.
S–T segment elevation in V4R, V1, V3, and V5.
T wave inversion in V4R, V1, V3, V5.
The position of the heart. (Defined as vertical if lead VL showed a dominant negative deflection, and horizontal if a dominant positive deflection.)
Dominant R wave in lead VR.
The presence of P waves suggesting right atrial hypertrophy. (Right atrial P waves: pointed P waves of 2·5 mm. or more.)
The incidence of supraventricular arrhythmia.

Prominent Q waves in leads VL, VF, and præcordial leads, indicative of infarction.
Splintering of the QRS complex in præcordial leads (qrS pattern), suggestive of infarction.
The presence of bundle-branch block.

Cardiographic Signs in Groups 1 and 2. There was no significant difference between the cases with lone right ventricular hypertrophy and those with combined hypertrophy, which is not surprising as in the latter group the right ventricle dominated the left. All cases had a dominantly negative deflection, and the majority an rS complex, in V5.

There was wide variation in the amplitude of R and S waves in the præcordial leads studied, and no conclusions could be drawn. The R/S ratio in V4R and V1, exceeded unity in less than half the cases, and there was no difference between the two groups in V4R, although in V1, the ratio was more often in excess of 1 in the cases with lone right, than in those with combined, hypertrophy (Fig 1, 2, and 3).

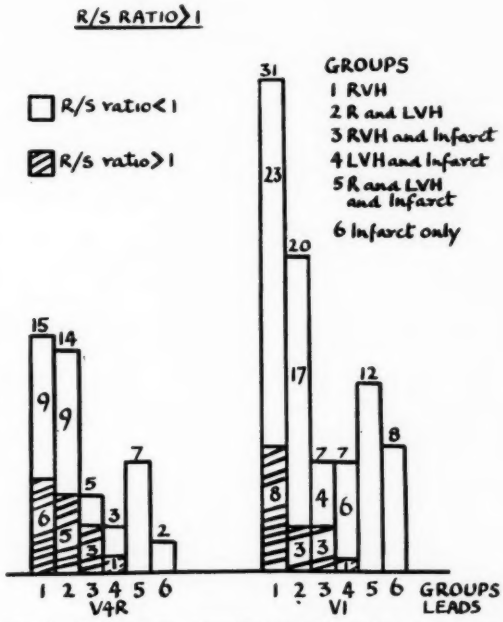


FIG. 1.—Histograms, showing the ratio of R to S waves (R/S ratio) in leads V4R and V1 in all groups.

The S–T segment was iso-electric in V1 and V5 in the majority of cases in both groups; when it was elevated, the elevation never exceeded 2 mm. in lead V5 with the exception of one case with right bundle-branch block due to lone right ventricular hypertrophy, in which the S–T segment was 4 mm. elevated (Table II, Fig. 4).

The T waves were inverted, flat, or biphasic in the majority of cases in both groups in V4R and V1, and positive in the majority in V5 (Table II).

Splintering of the QRS complex in præcordial leads (QRS pattern) was seen in only one case, a patient with lone right ventricular hypertrophy, in lead V3 (Fig. 2).

Tiny q waves preceding an rS complex in V5 were found in two cases with lone right ventricular hypertrophy.

The position of the heart was vertical in the majority of cases in both Groups 1 and 2, being slightly more frequent in Group 2 (Fig. 2 and 3).

A "right atrial" P wave was present in a minority of cases in both groups (Fig. 2).

Three cases in Group 1 and one in Group 2, had right bundle-branch block.

A dominant R wave in lead VR was seen in 13 cases (42%) in Group 1 and 8 cases (40%) in Group 2.

The Form of the Ventricular Complex in Leads V3 and V5 in the 34 Cases with Infarction. The ventricular complex in V5 was of three types. *Type A* was typical of infarction with wide deep Q waves, elevated S–T segment, and inverted T waves (15 cases). *Type B* (4 cases) was highly

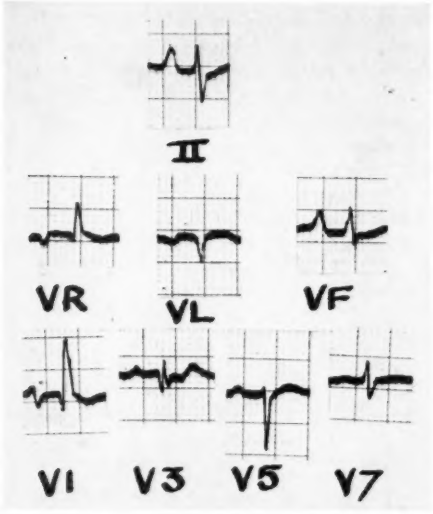


FIG. 2.—Cardiogram of patient with lone right ventricular hypertrophy without cardiac infarction. The P wave in lead II is 3 mm. in height and pointed. VR shows a qR pattern. V3 shows a QRS pattern with a deep Q wave suggestive of septal infarction. V5 shows an rS pattern. The heart is vertical in position.

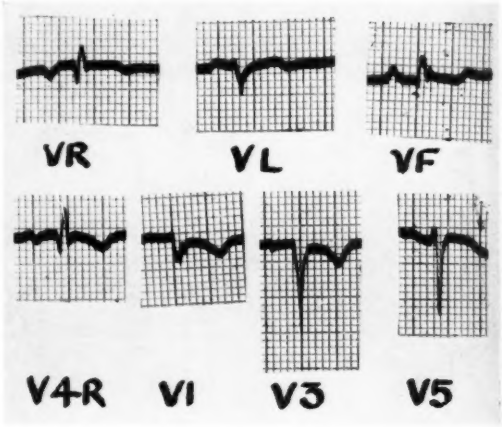


FIG. 3.—Cardiogram of patient with combined ventricular hypertrophy. There is a deep S wave in V5 with inversion of the T wave; qR in V4R, and rSR in VR. The heart is vertical in position.

TABLE II

S–T SEGMENT AND T WAVE CHANGES IN V5 IN 85 CASES

	Group	S–T elevation		T wave flat, biphasic, or inverted		Total patients
Hypertrophy only	1 2	18	35%	17	33%	51
Hypertrophy and infarction	3 4 5	17	68%	8	31%	26
Infarct only	6	7	88%	5	63%	8

suggestive but not diagnostic, and consisted of very small or "embryonic" r waves in V5 (which were smaller than those in V3), flattening or inversion of the T wave, and slight S–T elevation. Resemblance to right ventricular hypertrophy was seen in the form of a qR pattern in VR in some cases. *Type C* was frankly equivocal and consisted of an rS pattern with negative, flat or positive T

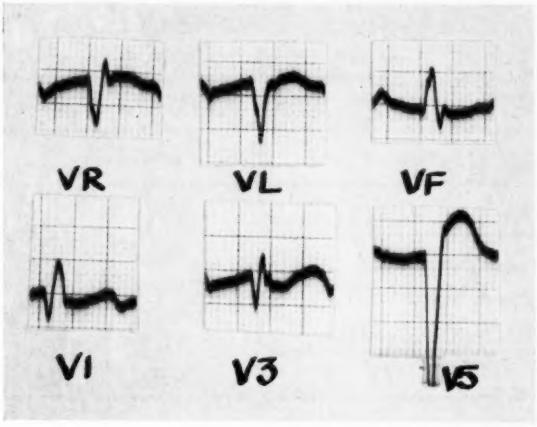


FIG. 4.—Cardiogram of patient with lone right ventricular hypertrophy without infarction. Right bundle-branch block is present, and V5 shows a qS pattern, with S–T segment elevation of 4 mm, suggesting infarction.

wave, and S–T elevation not exceeding 2 mm. This was often the only abnormality in the cardiogram, which therefore resembled that of lone or dominant right ventricular hypertrophy. Fig. 5 shows diagrammatically examples of the types of complex found, and Fig. 6A, B, and C illustrates typical cardiograms.

Type A was more frequently found in cases with infarction without ventricular hypertrophy and the converse was also true. Table III sets out the infarct groups (3, 4 5, and 6) in relation to the cardiographic types A, B, and C.

If all the cases with associated ventricular hypertrophy are grouped together and compared with those with infarct alone, the χ^2 test gives a figure of 4·05, which, when corrected, falls to 2·58, which is below the significance level, but nevertheless shows some trend which suggests that associated ventricular hypertrophy modifies the characteristic pattern of anterior infarction.

TABLE III

TYPES OF CARDIOGRAM AMONG ALL GROUPS WITH INFARCTION

Infarct groups	Cardiographic type		
	A	B+C	Total
3 RVH+I	2	5	7
4 LVH+I	2 } 9	5 } 17	7 } 26
5 R and LVH	5	7	12
6 I only	6	2	8

Site of the Infarct and Cardiographic Type. Antero-septal infarcts were present in 26 of the 34 patients; in 12 of them the cardiogram was of Type A, and in 14 of types B, or C (Table IV).

The Size of the Infarct. It was not possible to grade the size of the infarct with accuracy, but it was regarded as large when it involved an appreciable portion of the anterior wall and extended into the septum or posteriorly. Of 16 large infarcts 9 were associated with classical signs of the disease (Type A) and 7 with the rS patterns (Types B and C). Of the 18 less extensive infarcts 6

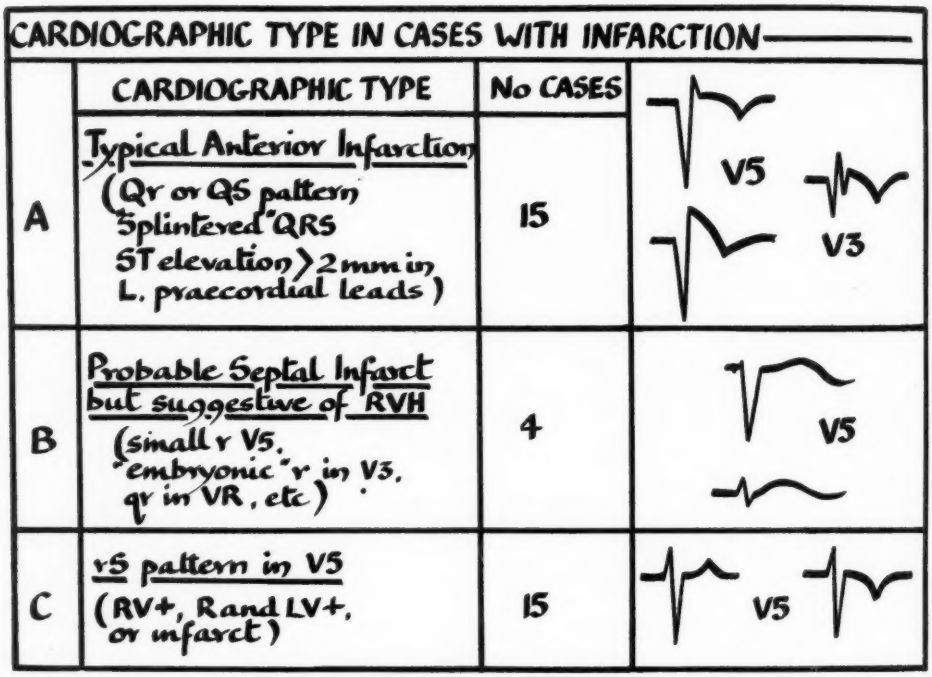


FIG. 5.—Diagrammatic table illustrating the types of complex in lead V5 in 34 cases with infarction. In cardiographic type A (typical anterior infarction) out of 15 cases, two had equivocal præcordial leads but a diagnostic pattern in VL and VF respectively.

TABLE IV

RELATION OF CARDIOGRAM TO SITE OF INFARCT IN 34 PATIENTS

Site of infarct	Cardiographic type		
	A	B+C	Total
Antero-septal	12	14	26
Antero-lateral ..	1	2	3
Posterior	1	1	2
Subendocardial ..	0	2	2
Scattered fibrosis with ventricular aneurysm	1	0	1
Total	15	19	34

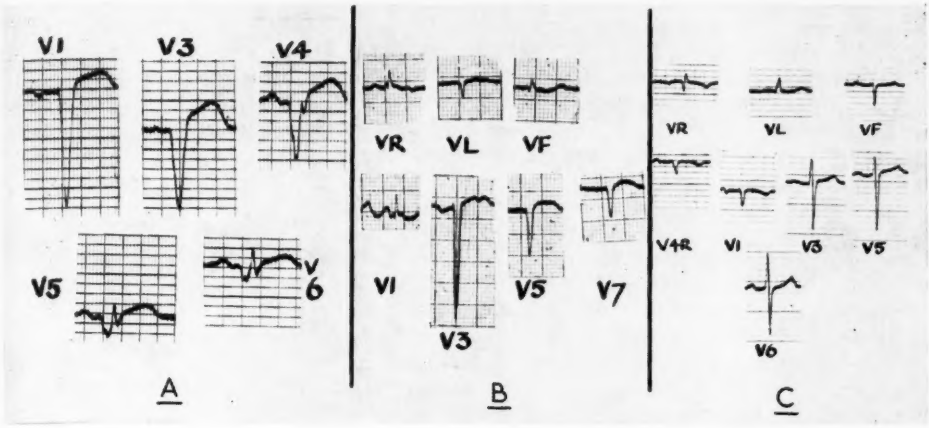


FIG. 6.—(A) *Classical infarction pattern* (*Type A. Fig. 5*) in a patient with anterior infarction without ventricular hypertrophy. There is a Qrs pattern in V5 with elevation of the S–T segment. Leads V3, 4, 6, also show evidence of infarction (each large square=0·1 sec.). (B) *Equivocal pattern* (*Type B. Fig. 5*) in a patient with lone right ventricular hypertrophy and anterior infarction. The dominant R in VR and V1, and the vertical position of the heart indicate right ventricular hypertrophy, and the rS pattern in V5 is in harmony. However, the reduction in size of the r wave from V3 to V7, and the S–T elevation suggests the possibility of infarction (each large square=0·2 sec.). (C) *rS pattern* (*Type C. Fig. 5*) in a patient with combined ventricular hypertrophy and anterior infarction. There is nothing to suggest the presence of infarction other than the association of the rS pattern in V5 with a horizontal heart, which could be due merely to the combined hypertrophy. The infarction is thus concealed (each large square=0·1 sec.).

had the classical pattern and 12 the rS pattern. Equivocal signs were therefore more common when the lesion was restricted, but large infarctions were frequently associated with the rS pattern in V5.

There were two instances of subendocardial infarction in the series and both were associated with equivocal cardiographic patterns (Table IV).

An attempt was made to determine the influence of the age of the lesion on the cardiographic pattern; but this proved difficult because of the presence of multiple infarcts, both old and recent, in some cases. There did not, however, appear to be any relation between the age of the infarct and the cardiographic type; but as will be seen later, healing was associated with the development of an rS pattern in lead V5 (Fig. 7, A, B).

Cardiographic Findings in the Cases with Infarction (*Groups 3 to 6*)

There were no significant differences between the amplitudes of R and S waves in V4R, V1, V3, and V5 in these groups and in Groups 1 and 2.

Lead V4R was recorded in 5 of the 7 cases in Group 3 (infarct and RVH) and in 3 of these the R/S ratio was greater than unity. The ratio in V1 was greater than unity in 3 of the 7 cases in the same group (Fig. 6B). In Group 4, the ratio was greater than unity in two cases, one in V4R and one in V1 (Fig. 1). It was never greater than unity in Groups 5 and 6 in either lead (Fig. 7).

The S–T segment was iso-electric in V1 in the majority of cases in all groups except Group 4 (LVH and infarct). In V5 there was elevation of the S–T segment in the majority of cases in all infarct groups. This contrasts with the presence of S–T segment elevation in the minority of cases in Groups 1 and 2 (RVH, R, and LVH). The S–T elevation was most frequent in cases with infarction only (Table II). No conclusions could be drawn about individual cases. The degree of S–T elevation was greater in the groups with infarction than in those with hypertrophy alone. Thus

the maximum S–T elevation in infarction was 7 mm. in V3, and 5 mm. in V5, as compared with 4 mm. in V3, and 2 mm. in V5 in the hypertrophy cases, with the exception of the patient with bundle-branch block (Fig. 4 and 8A, B, and C).

In lead V4R or V1 the T waves were usually positive in the infarction cases, instead of negative, flat, or biphasic as in those with hypertrophy. In lead V5, however, the T wave was positive in the majority of cases of all groups, except Group 6 (Table II). This was true even when lone left ventricular hypertrophy was associated with infarction, when T wave inversion might especially have been expected in a left præcordial lead. The presence of T wave inversion in V5 usually suggested infarction (Fig. 9B), but inversion of the terminal portion of the T wave occurred in one instance with lone right ventricular hypertrophy (Fig. 9A).

Right bundle-branch block was found once in Group 3, left bundle-branch block once in Group 4 and twice in Group 5, and intraventricular block once in Group 3 and once in Group 4.

The position of the heart was vertical in only 4 of the 34 cases (12%) with infarction (three in Group 3 and one in Group 4), as compared with 34 of the 51 (66%) with hypertrophy alone.

A right atrial P wave was not found in any patient with infarction, although it occurred in 13 of the 51 who had hypertrophy alone (Fig. 2). A dominant R wave in VR was found in 3 out of 7 cases in Group 3, 3 out of 5 in Group 4 (VR was not recorded in one instance), 3 out of 12 patients

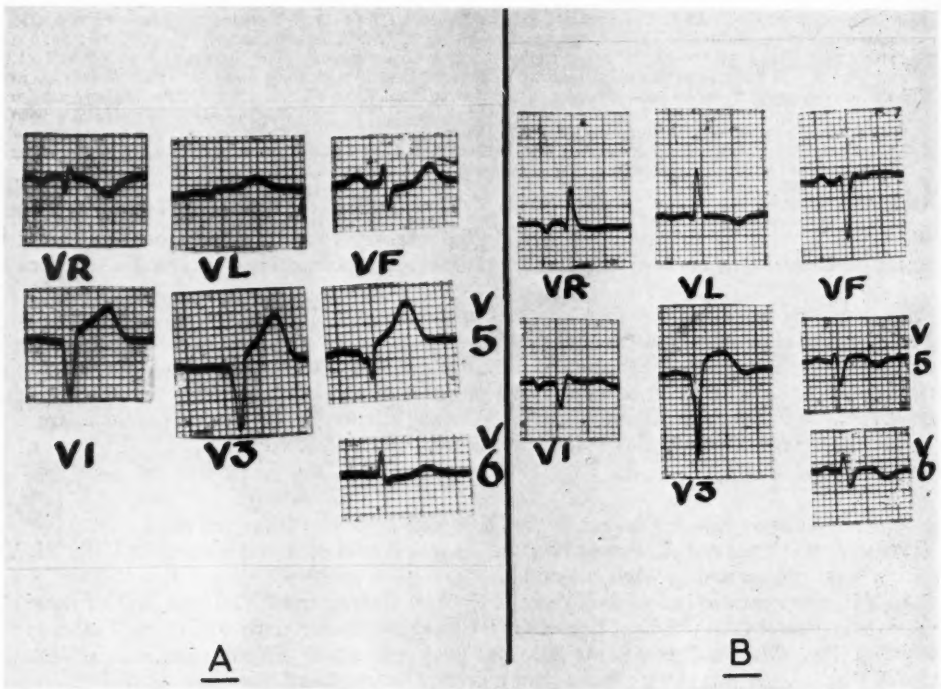


FIG. 7.—(A) Cardiograms from a patient with acute anterior infarction. There is S–T elevation in leads VL, V1, V3, and V5, with positive T waves. A rudimentary secondary r wave can be seen in V5. (B) 7 days later, the rudimentary r in V5 has grown, the q has disappeared, the S–T elevation is less, and the T wave has become inverted. There is also T wave inversion in V3–6, and VL. VR now shows a dominant R wave. The appearances are compatible with right ventricular hypertrophy. At autopsy there was occlusion of the descending branch of the left coronary artery with extensive anterior infarction, and early aneurysm formation of the left ventricle.

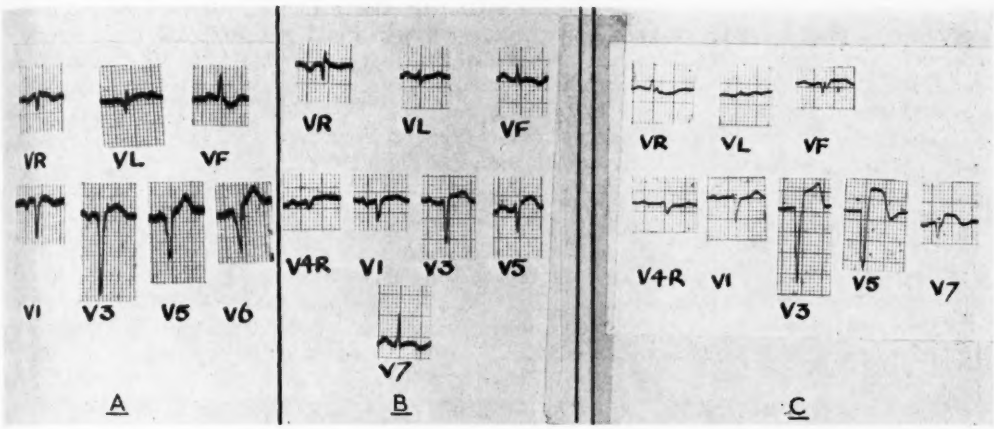


FIG. 8.—(A) Cardiogram of a patient with lone right ventricular hypertrophy without infarction. Leads V3–V6 show a qS pattern. The S–T segment is elevated 2 mm. in V5, and the T wave is upright. VL shows a q wave which is probably reciprocal to the R in VF. The pattern, however, is highly suggestive of infarction, but the heart is vertical in position. (B) Cardiogram of a patient with combined ventricular hypertrophy and anterior infarction. V5 shows the rS pattern, and there is S–T elevation of 2·5 mm. The heart is semi-vertical in position. (C) Cardiogram of a patient with combined ventricular hypertrophy and anterior infarction. Lead V5 shows the classical Qr infarct pattern, with S–T segment elevation of 5·5 mm. VR shows a dominant R wave, and VF a deep Q. Ventricular hypertrophy has not influenced the classical pattern of infarction.

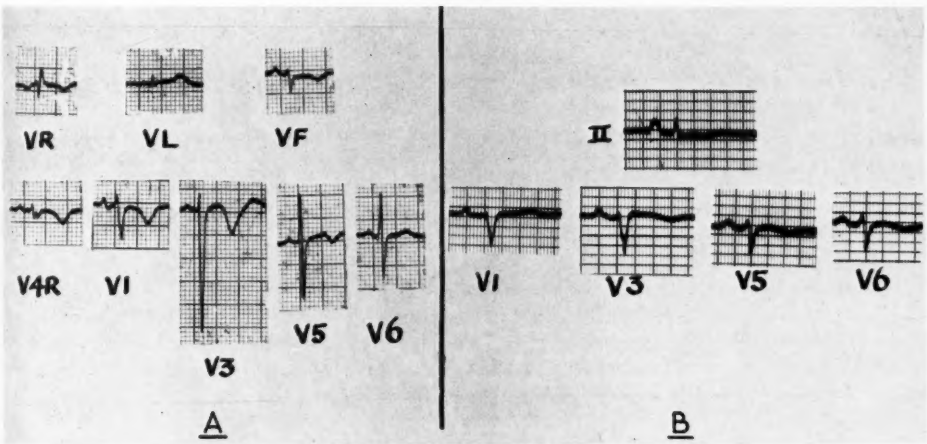


FIG. 9.—(A) Cardiogram of a patient with lone right ventricular hypertrophy, showing T wave inversion from V4R to V5. The heart is horizontal. (B) Cardiogram of a patient with combined ventricular hypertrophy and anterior infarction. The T waves are also inverted in the chest leads.

in Group 5, and 2 out of 8 in Group 6. It thus occurred even in the absence of ventricular hyper trophy and was of no value in distinguishing hypertrophy from infarction. The dominant R in VF occurred in only 3 of the 5 cases with ventricular aneurysm and was presumably reciprocal t the dominant negative deflections in left præcordial leads. These findings (Fig. 10) support thos of East and Oram (1952), who showed that aneurysm can occur in the absence of this sign, in spit of the views of Goldberger and Schwartz (1948).

The important differential signs between infarction and hypertrophy were right atrial P wave and a vertical position of the heart, a combination that did not occur in infarction without hyper trophy. Right atrial P waves were also absent when infarction was accompanied by hypertrophy and a vertical heart was seen only in 12 per cent of these cases, in contrast to 66 per cent whe hypertrophy alone was present.

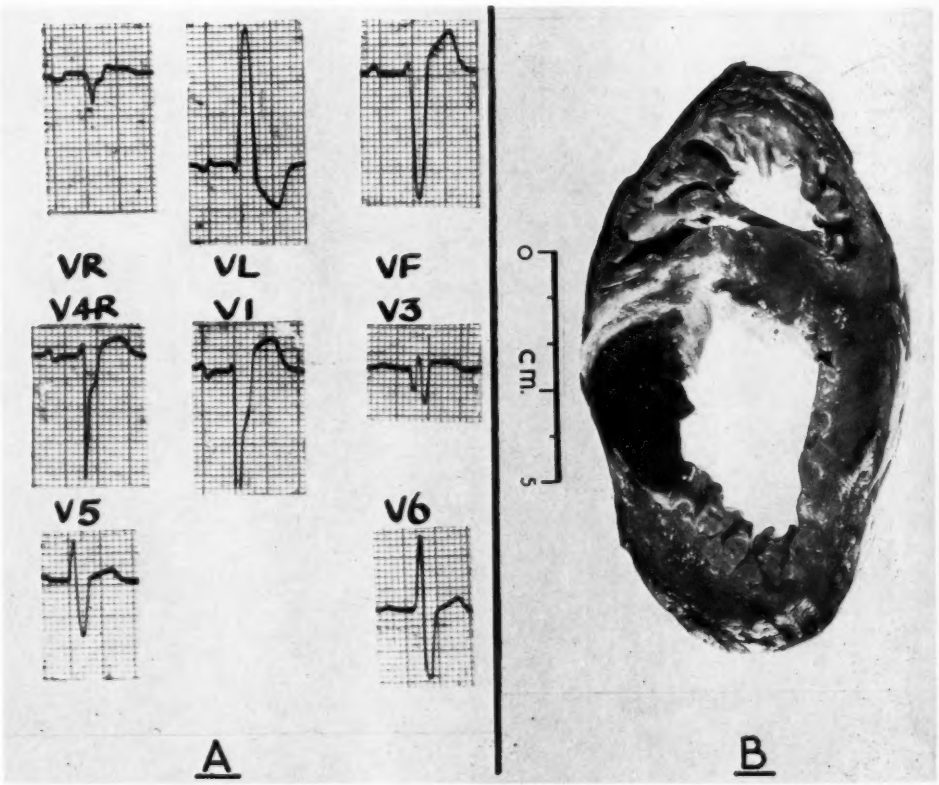


FIG. 10—(A) Cardiogram of a patient with right ventricular hypertrophy, large anterior infarction, and early cardiac aneurysm. Intra-ventricular block is present. There is a deep q in V3, but V5 and 6 show the rS pattern. The heart is horizontal. (B) Pathological specimen showing infarction, subendocardial thrombus, and early ventricular aneurysm.

Discussion and Conclusions

These results indicate that in certain circumstances the cardiographic picture of anterior cardiac infarction may be indistinguishable from that of dominant or lone right ventricular hypertrophy, and that the cardiogram of the latter condition may closely simulate that of cardiac infarction. It is clear that often the differential diagnosis cannot be made with certainty, but certain diagnostic pointers may be of value. Where there is an rS pattern in V5 there may be diagnostic evidence of infarction in other leads (V3, VL, or VF) and this should always be sought. In the absence of such evidence, a negative T wave in V5 and positive T wave in V4R, or V1, S–T segment elevation greater than 2 mm., or a small Q wave preceding the rS complex, are all suggestive of infarction. The r wave that fails to "grow" across the præcordial leads from right to left, or becomes smaller, is of course a well-known sign of infarction in the septal region.

By contrast, a vertical position of the heart, and "right atrial" P waves suggest lone or dominant right ventricular hypertrophy and make infarction unlikely. A dominant R wave in VR may occur in ventricular hypertrophy with or without infarction; it may be seen with infarction alone, but is rather more frequent in its absence. When associated with infarction it does not necessarily indicate ventricular aneurysm, nor is it essential for this diagnosis. An R/S ratio greater than unity in V4R, or V1, positive T wave in V5 and negative in V4R or V1, and S–T elevation less than 2 mm. in V5 all support hypertrophy rather than infarction, but are by no means exclusive of the latter. The differential diagnosis can best be made by considering all the possible combinations of cardiographic signs.

It is clear that cardiograms showing the rS pattern in V5 should be interpreted with great caution, and the possibility of a concealed infarct considered. Indeed, this electrocardiogram should probably be regarded as one of the variants representing cardiac infarction, bearing in mind the fact that it may be found in the absence of infarction, and very rarely even in the apparently normal heart.

The Genesis of the rS Pattern. It is generally considered that the rS pattern in V5 represents extreme clockwise rotation of the heart around the vertical axis, the usual cause being hypertrophy of the right ventricle (Goldberger, 1947; Sokolow and Lyon, 1949; Myers *et al.*, 1948; Pagnoni and Goodwin, 1952).

The results of the present investigation show that this complex can occur under varied circumstances and suggest that the concept of clockwise rotation may be an over simplification that requires further examination. The assumption that præcordial leads record a pure pattern of the electrical events occurring in the muscle that they face has been criticized (Scherlis *et al.*, 1951; Milnor *et al.*, 1953; Grishman *et al.*, 1953; Camerini *et al.*, 1956). Wilson *et al.* (1944) pointed out that although excitation of the muscle in contact with the exploring electrode produces a much larger deflection than that of an equal muscle mass at a greater distance from it, activation of all parts of the ventricular myocardium contributes to the complex derived from any electrode. In other words, the balance of electrical forces throughout the whole myocardium, and not merely the localized activity, will effect any given electrode. The deep S wave in V5 might be explained by rotation of the horizontal loop of ventricular depolarization in right ventricular hypertrophy. (Lasser *et al.*, 1951; Grishman *et al.*, 1953; Shillingford and Brigden, 1954). Such rotation must be mediated by a number of factors, including alteration of the relative position of the two ventricles due to the increased size of the right, the magnitude of the respective forces of the two ventricles, and the direction and spread of the impulse. Alteration in position of the septum and changes in its electrical activity due to infarction may also play a part.

From the practical aspect the commonest cause of a deep S in V5 is right ventricular hypertrophy, either solitary or in association with lesser degrees of left hypertrophy. As has been shown, many cases of right ventricular hypertrophy do not show a dominant R wave in V4R or V1, and in some but not all instances, this is due to the presence of associated left ventricular hypertrophy which suppresses the right præcordial R wave. In the present series, the existence of added left

ventricular hypertrophy was not associated with increased amplitude of S waves in right præcordial leads, probably because of the deep S in V5.

The factors concerned in the production of the complex in V5 in infarction require elucidation. Several possible explanations may be considered.

The Age of the Infarct and the Healing Process. It might be supposed that the rS complex represents partial healing of the infarct, with disappearance of the Q wave, but only partial "recovery" of the r wave. Fig. 7 shows that this suggestion is at least feasible, since in the second cardiogram the S–T elevation and q wave had disappeared, to be replaced by the rS pattern. However, this hypothesis does not explain the deep S wave, nor is the rS pattern confined to "old" infarcts, and other factors must be involved.

The Influence of Ventricular Hypertrophy. The results strongly suggest that hypertrophy of the right ventricle modifies the classical infarction pattern in V5. When right ventricular hypertrophy is present, the loop of the QRS vector is orientated to the right and posteriorly in the horizontal projection, while in left ventricular hypertrophy the loop is orientated to the left and posteriorly. In typical anteroseptal infarction, the loop is directed to the left, with disappearance of the right anterior initial portion of the loop due to antero septal activation. This results in Q waves from anteroseptal præcordial leads (Grishman *et al.*, 1953). It seems possible that previous rotation of the loop to the right by right ventricular hypertrophy might result in the disappearance of anterolateral negative vector forces of infarction, and thus the replacement of the q wave by a small r wave in V5. A similar explanation might hold when lone left ventricular hypertrophy is present in association with infarction, but the mechanism is obscure and further deductions cannot fairly be made.

The Site and Size of the Infarct. In the majority of patients the infarcts were anteroseptal, but subendocardial, lateral and even posterior lesions occurred in a few cases. It is probable, however, that the rS pattern in infarction in V5 depends mainly upon septal involvement, with consequent disorientation of normal septal vectors. The size of the infarct apparently has no great bearing, since both large and small ones were found in association with the rS pattern.

The thickness of the ventricular wall involved may be of some importance. rS patterns in V5 were found in the two cases with subendocardial infarction. It is known that q waves may not develop in subendocardial infarction (Prinzmetal *et al.*, 1953) while the rS pattern has been found in subepicardial infarction involving the posterolateral wall of the left ventricle by Levy and Hyman (1950), who noted that . . . "since the spread of excitation from the endocardium outward is not affected in this type of lesion, a Q wave will not appear, and only a reduction in amplitude of the R wave or the appearance of an S wave in the leads which face the infarcted area may occur. . . ."

Intramural infarction extending neither to endocardium nor epicardium may also fail to produce a characteristic Q wave. Many of the cases in the present series were studied retrospectively and it was not always possible to discover the thickness of the infarcted ventricular wall from the necropsy reports.

The findings in the series studied here suggest that the most important factors concerned with the production of an rS pattern in V5 in anterior infarction are associated ventricular hypertrophy (usually dominantly right) and changes of healing in the infarct, which may be cardiographically surprisingly rapid (Fig. 7).

The rarity of a vertical heart position in association with infarction suggests that this is an important differential diagnostic point between ventricular hypertrophy and infarction. A horizontal position does not indicate infarction, but a vertical position makes this diagnosis improbable, though it does not exclude it. Possibly the presence of anterior infarction rotates the QRS vector to the left in the frontal plane despite the presence of right ventricular hypertrophy, thus preventing the "vertical" position from developing. A right atrial P wave may possibly exclude infarction, for it was not seen in any case in this series.

The term clockwise rotation should probably be abandoned in favour of the term "rS complex in V5", which may be due to lone right ventricular hypertrophy, dominant right ventricular hypertrophy, anterior infarction, or a combination of all. Occasionally, it may even be a normal finding

The results show not only the cardiographic resemblance of infarction to right ventricular hypertrophy, but also that of right ventricular hypertrophy to infarction (Myers, 1950). Fig. 2 shows a prominent Q in V3, with rS in V5, apparently diagnostic of septal infarction, yet none was found at necropsy. Clearly, alteration of the position of the two ventricles, of the septum, and of the balance of forces due to right ventricular hypertrophy, may re-orientate the projection of the QRS vector in the horizontal plane in a fashion similar to that produced by septal infarction, thus counterfeiting the cardiogram of the latter.

Summary

The causes of an rS complex in lead V5 have been investigated by the study of necropsies on 85 patients all of whom had a predominantly negative deflection in that lead.

A predominantly negative deflection in V5 was seen in lone right ventricular hypertrophy, in combined ventricular hypertrophy, and in hypertrophy with anterior cardiac infarction. The typical patterns of anterior infarction were less common when ventricular hypertrophy was present than when infarction occurred in the absence of right ventricular hypertrophy. Close resemblance was found between the electrocardiogram of right ventricular hypertrophy and that of anterior infarction. The differential diagnosis is discussed, and also the reason for the replacement of the classical infarct pattern in V5 by the rS pattern.

I am indebted to Mrs. Angela Birbeck for the diagrams, to Mrs. Joyce for help in collecting cardiographic material, and to Mr. Brecknell and the staff of the Department of Medical Illustration for the illustrations.

References

Bain, C. W. C., and Redfern, E. M. V. (1948). *Brit. Heart J.*, **10**, 9.
Camerini, F., Goodwin, J. F., and Zoob, M. (1956). *Brit. Heart J.*, **18**, 13.
East, T., and Oram, S. (1952). *Brit. Heart J.*, **14**, 125.
Goldberger, E. (1947). *Unipolar Lead Electrocardiography*. Henry Kimpton, London.
——, (1949). *Amer. J. Med.*, **7**, 756.
——, and Schwartz, S. P. (1948). *Amer. J. Med.*, **4**, 243.
Grishman, A., Scherlis, L., and Lasser, R. P. (1953). *Amer. J. Med.*, **14**, 184.
Lasser, R. P., Borun, E. R., and Grishman, A. (1951). *Amer. Heart J.*, **42**, 370.
Leatham, A. (1950). *Brit. Heart J.*, **12**, 213.
Levy, L., and Hyman, A. L. (1950). *Amer. Heart J.*, **39**, 243.
Milnor, W. R., Talbot, S. A., and Newman, E. V. (1953). *Circulation*, **7**, 545.
Myers, G. B. (1950). *Circulation*, **1**, 860.
——, Klein, H. A., and Stofer, B. E. (1948). *Amer. Heart J.*, **35**, 1.
——, ——, —— (1949). *Amer. Heart J.*, **37**, 374.
——, ——, ——, and Hiratzka, T. (1947). *Amer. Heart J.*, **34**, 785.
Pagnoni, A., and Goodwin, J. F. (1952). *Brit. Heart J.*, **14**, 451.
Prinzmetal, M., Kennamer, S. R., Shaw, C. McK., Kimura, N., Lindgren, I., and Goldman, A. (1953). *Circulation*, **7**, 1.
Scherlis, L., Lasser, R. P., and Grishman, A. (1951). *Amer. Heart J.*, **42**, 235.
Shillingford, J., and Brigden, W. (1954). *Brit. Heart J.*, **16**, 13.
Sokolow, M., and Lyon, T. P. (1949). *Amer. Heart J.*, **38**, 273.
Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossmann, C. E., Hecht, H., Cotrim, N., Menezes de Oliveira, R., Scarsi, R., and Barker, P. S. (1944). *Amer. Heart J.*, **27**, 19.
——, Rosenbaum, F. F., and Johnston, F. D. (1947). *Advanc. intern. Med.*, **2**, 1.

DIGITALIS AND INTRACTABLE HEART FAILURE

BY

EVAN FLETCHER AND C. F. BRENNAN

From the Belfast City Hospital

Received June 5, 1957

Judicious digitalis therapy still remains the most important factor in the management of congestive heart failure at all its stages. Digitalis acts directly on the heart muscle, increasing the output of the failing heart in the presence of congestion, thereby restoring cardiac compensation (Harvey *et al.*, 1949). As a result, therapeutic doses slow the pulse. Dosage required for adequate digitalization cannot be predicted with certainty, although body weight may be a guide (Eggleston, 1915). Therapeutic trial alone may indicate if digitalis is likely to be beneficial. Moreover, experience shows that digitalis requirements may vary from time to time during the course of congestive heart failure: any procedure that helps to determine these for patients requiring urgent help is a significant therapeutic advance, as it provides a basis for rational therapy. We have used the digitalis tolerance test (Lown and Levine, 1955) in assessing the digitalis requirements of nine cases of intractable congestive heart failure. Therapy based on the results benefited the patients, and allowed us to make certain deductions, which we believe to be important, about the nature of disturbances of rhythm occurring in congestive failure and their management.

It may be opportune at this stage to examine some of the important factors that play a role in the evolution of intractable congestive failure in so far as they affect digitalis therapy. A profound relationship exists between potassium metabolism and digitalis toxicity (Lown *et al.*, 1951) with regard to the action of the drug on isolated groups of cardiac cells producing ectopic foci. Depletion of myocardial potassium sensitizes the heart to digitalis, so narrowing the margin between its therapeutic and toxic action. Potassium loss may render a therapeutic dose a toxic dose. During the development of congestive failure, total body potassium is reduced (Burrows and Sisson, 1950). A negative potassium balance is also favoured by nutritional problems in advanced congestive failure—poor appetite, monotonous diets, nausea, impaired absorption, and deranged liver function. Perhaps most important of all, therapeutic measures aimed at reducing the work of the heart may be responsible for substantial potassium loss, e.g. rigid salt restriction and administration of ammonium chloride during mercurial diuresis (Lesser *et al.*, 1952). In addition diamox (Berliner *et al.*, 1951), steroid hormones (Lown *et al.*, 1951), ion exchange resins, and mechanical fluid drainage (paracentesis, acupuncture) deplete body stores of potassium. It would appear that the above factors play an important part in the evolution of intractable congestive failure as they may adversely modify the response of the heart to digitalis. In this connection also special reference must be made to coronary arterial disease. There is experimental evidence to show that myocardial ischæmia is associated with loss of intracellular myocardial potassium (Dennis and Moore, 1938). The progressive loss of myocardial potassium associated with advancing coronary disease may help to explain the changing sensitivity of the heart to digitalis. Toxic doses of digitalis may also deplete the myocardial cells of potassium (Calhoun and Harrison, 1931) and potassium administration will abolish toxic arrhythmias caused by digitalis (Sampson *et al.*, 1943). We have utilized the complex relationship between digitalis and potassium metabolism in the management of our cases.

This paper is concerned with the particular problem of the digitalis status of patients admitted to hospital with intractable heart failure. Enquiry often reveals a long history of congestive failure, often for months or years, with varying response to digitalis and diuretic treatment. Frequently the

dosage of digitalis given before admission cannot be ascertained, or the drug may have been omitted some time before the patient is seen, on account of some complicating factor. We submit that the decision to administer more digitalis or to withhold the drug in such cases amounts to a medical emergency. Our results with the acetyl strophanthidin test support the view that many of these cases can be regarded as cases of "failed digitalis treatment." When adequate digitalization is instituted striking improvement may occur. Clinical assessment alone has limitations. The physician may be hard put to differentiate the nausea and vomiting of congestion of the abdominal viscera from the more ominous sickness of digitalis intoxication due to the central emetic action of the drug (Hatcher and Weiss, 1922). Tachycardia certainly does not exclude serious digitalis intoxication (Heyl, 1932; Levine, 1948) and it may be impossible to decide even with electrocardiographic analyses if ectopic beats are toxic in origin or due to underlying organic heart disease. A trial dose of the usual digitalis preparations may be hazardous in the presence of potential digitalis intoxication. At any rate the correct dosage is conjectural, oral therapy may be ineffective on account of nausea and vomiting, and resort to intravenous administration of digitalis in a patient who may have already received an unknown quantity of the drug is not justifiable. Even the most rapidly acting preparations, ouabain, digoxin, and lanatocide C (cedilanid) may produce toxic effects in these cases (Lown and Levine, 1955). Nevertheless to withhold digitalis from a patient who urgently requires it may have as serious consequences as administration of the drug in the presence of digitalis toxicity. The acetyl strophanthidin test (Lown and Levine, 1955) seems to have answered the question of digitalis requirements in our cases of intractable congestive failure.

Acetyl strophanthidin is a synthetic ester of strophanthidin, an aglycone obtained from the seeds of *strophanthus kombé*. It is prepared ready for intravenous use as an alcoholic solution, each ml. containing 0·5 mg. of the drug (approximately equivalent to 3 cat units. Eli Lilly and Co.). Its pharmacological action is the same as that of the digitalis glycosides (Chen and Elderfield, 1942; Gold *et al.*, 1946; Greiner and Reilly, 1952; Root and Chen, 1953). However, the onset of its action is extremely rapid, and the commencement of its effect is noted within 5 minutes, 85 per cent within 10 minutes, and the full effect of the drug is almost completely dissipated within 4 hours. Thus acetyl strophanthidin can produce very rapid digitalization over a short period of time, which can be observed electrocardiographically.

Technique for Acetyl Strophanthidin Test

A solution of acetyl strophanthidin in 5 per cent glucose and water was prepared for intravenous injection, 0·5 mg. in every 10 ml. Saline solutions were not used, to avoid sodium administration in congestive heart failure. A drop of heparin was added to the syringe to prevent clotting. 2 ml. of the solution were administered every 5 minutes through the needle in an arm vein. Electrocardiographic records of an appropriate lead were taken at suitable intervals using a direct writer electrocardiograph. Occasionally the doses of acetyl strophanthidin were increased or given at shorter time intervals as warranted by electrocardiographic observation. Administration of the drug was stopped immediately if a therapeutic effect or a toxic effect was observed on the electrocardiograph, or if nausea occurred. Slowing of the heart rate was taken to indicate a therapeutic effect, and the production of abnormal rhythms a toxic effect. Interpretation of the test depended upon the amount of acetyl strophanthidin required to produce a result, and the nature of change in heart rate and rhythm. Throughout the period of observation procaine amide was available in a syringe for intravenous administration in the event of digitalis toxicity of severe degree.

Case Reports

Case 1. Digitalis indicated. A man, aged 77 years, was admitted with advanced congestive heart failure due to coronary artery disease. Congestive heart failure had been present for six months, and he had received digitalis in varying doses with mercurial diuretics. Because of nausea and vomiting he dreaded taking digitalis. On examination the pulse was rapid (rate 123) and irregular. There was gallop rhythm, and evidence of pulmonary œdema. B.P. 150/90. An electrocardiogram

appeared to confirm the presence of complete left bundle-branch block, and sinus rhythm complicated by the occurrence of very frequent ventricular extrasystoles of varying shape, usually considered typical of digitalis intoxication (Scherf and Schott, 1953). Serum potassium 4·5 m.eq. per litre. On account of the intense nausea and vomiting, and the occurrence of multiform ventricular extrasystoles, and the patient's apparent "intolerance" to oral digitalis (he refused to take the drug), it was decided that no further digitalis should be given. During the succeeding five days his condition deteriorated, the pulse remained rapid, and attacks of cardiac asthma became more frequent. The patient was persuaded to co-operate. 0·25 mg. was administered orally every six hours. After twenty-four hours tachycardia with pulsus bigeminus occurred, and severe nausea and vomiting. The digitalis was promptly stopped and potassium chloride 5 g. administered daily by mouth in divided doses to combat what appeared to be digitalis intoxication. Two days later the patient's condition was unchanged. Thus clinical observation alone based on therapeutic trial failed to indicate his digitalis status, with a view to further treatment. Consequently an acetyl strophanthidin test was carried out. A total of 0·85 mg. acetyl strophanthidin was administered over a period of 70 minutes. The results are shown in Fig. 1. Acetyl strophanthidin caused an abrupt slowing of the heart rate from 123 to 68 a minute. Extrasystoles were completely abolished. The patient experienced no nausea whatever during the test.

Interpretation. Digitalis administration was urgently required for the following reasons: (i) The sudden slowing of the heart rate suggests that the persistent tachycardia was due to an ectopic auricular pacemaker which was suppressed by acetyl strophanthidin, restoring sinus rhythm. Thus the tachycardia was not a feature of congestive failure *per se.*, but rather an important aggravating cause of failure. (ii) The extrasystoles, although often bidirectional (Fig. 1) were not due to digitalis toxicity. They were abolished by acetyl strophanthidin when the heart rate was slowed. (iii) Nausea and vomiting were not due to the central emetic action of digitalis, but were the result of local gastro-intestinal changes associated with congestive failure, no doubt aggravated by local irritation of oral digitalis preparations. Consequently the patient was given digoxin intravenously to produce rapid digitalization and avoid nausea and vomiting. After 24 hours when 2·5 mg. digoxin had been administered, the pulse rate was slowed to 68 beats a minute, intraventricular conduction was improved, and no extrasystoles were noted. The patient's general condition improved. It was found possible to maintain digitalization by oral digoxin without nausea. Three weeks later after orthodox treatment for congestive failure he was able to get out of bed in comfort, and had not felt so well for months.

Case 2. Digitalis contra-indicated. A 59-year-old man was admitted with advanced congestive heart failure due to chronic bronchitis and emphysema. On examination he had anasarca, gallop rhythm, B.P. 160/90, serum potassium 4·7 m.eq. per litre. He had had repeated courses of digitalis and diuretic therapy for 18 months. Six weeks before admission he had been receiving 0·75 mg. digoxin orally each day and 2 ml. mersalyl twice weekly. But in spite of this treatment his condition deteriorated necessitating admission to hospital. He had no nausea or vomiting, and in spite of apparent adequate digitalis dosage there was sustained tachycardia. As his digitalis status was in doubt, an acetyl strophanthidin tolerance test was carried out; 1·8 mg. was administered over a period of one hour. Nausea and vomiting occurred, and the drug was immediately stopped. The heart rate was not significantly slowed, and very frequent multiform ventricular extrasystoles occurred, occasionally bidirectional.

Interpretation. Acetyl strophanthidin produced evidence of digitalis intoxication. Consequently further digitalis administration was omitted. All diuretics were stopped, and the patient given 5 g. potassium chloride orally in divided doses each day for three days. The patient's general condition improved. Breathing was easier and a slower normal sinus rhythm supervened. Subsequently the treatment was resumed by oral digoxin 0·25 mg. twice daily and diuretics were again started. The patient continued to improve and cardiac compensation was better than it had been for many months.

Case 3. Combined digitalis and potassium therapy indicated. A man, aged 77 years, was admitted with advanced congestive heart failure due to coronary artery disease. He had rapid uncontrolled auricular fibrillation, B.P. 230/130, gallop rhythm and cardiac asthma. Serum potassium 4·5 m.eq. per litre. Various courses of digitalis and diuretic therapy of indeterminate quantity for two

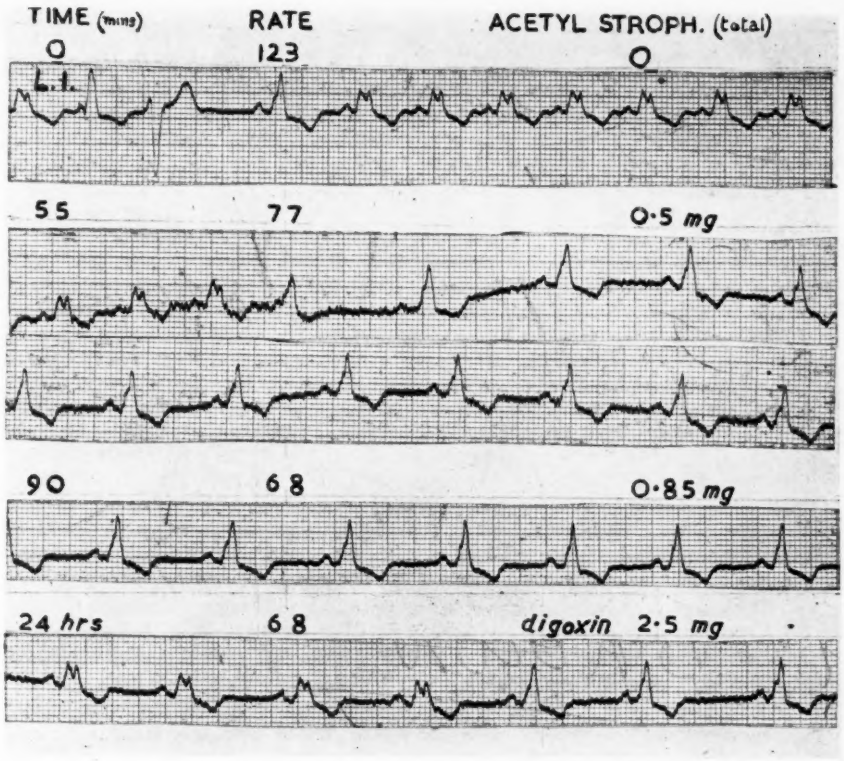


FIG. 1.—Case 1. Acetyl strophanthidin tolerance test. Therapeutic result. Restoration of sinus rhythm and abolition of ectopic beats.

years. He had been receiving 0·25 mg. digoxin twice daily by mouth and choledyl, but, his doctor had to omit digitalis a few days before admission on account of nausea and vomiting. The patient felt that he was unable to tolerate any form of digitalis. Nevertheless on account of the uncontrolled auricular fibrillation digitalis foliata gr. i was resumed thrice daily along with 2 ml. mersalyl twice weekly. A week later there was no improvement. Tachycardia persisted, and nausea and vomiting reappeared. Consequently it was decided that an acetyl strophanthidin test should be carried out to determine the digitalis status of the patient with a view to rational therapy. When a small dose of 0·4 mg. acetyl strophanthidin had been administered the ventricular rate had slowed from 166 to 80/90 beats a minute within half an hour (Fig. 2). The slowing was accompanied by the occurrence of very frequent multiform ventricular extrasystoles occasionally in groups. Acetyl strophanthidin administration was immediately stopped when the ectopic beats were noted, as they were the type considered typical of digitalis intoxication. No nausea was experienced during the test.

Interpretation. (i) The nausea and vomiting were not due to digitalis intoxication, but due to congestion of the abdominal viscera. (ii) Digitalis would slow the heart rate and would be required for that purpose. (iii) Digitalis might have produced extrasystoles and ventricular tachycardia. Consequently it was decided that digitalization should be carried out to slow the heart, and that potassium should be administered concurrently to suppress ectopic rhythms. Digitalis foliata gr. iii and potassium chloride 5 g. were given orally daily in divided doses while diuretic therapy was suspended. Seven days later the pulse rate was 70

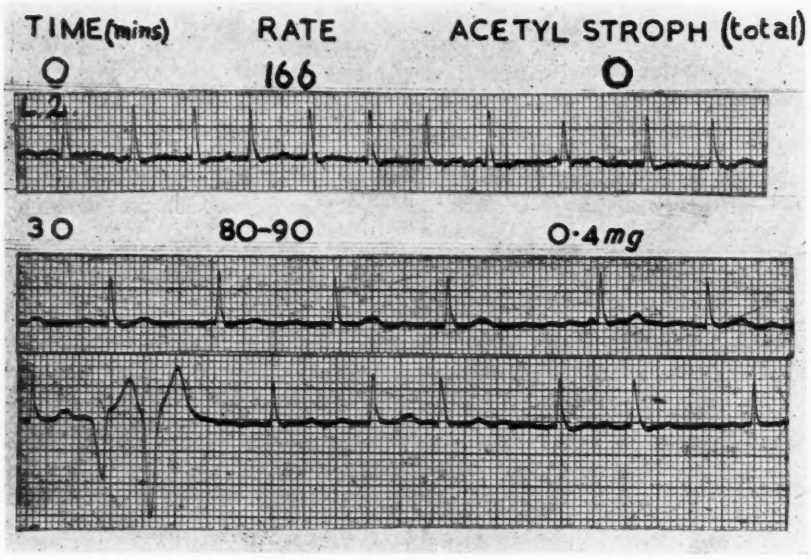


FIG. 2. Case 3. Acetyl strophanthidin tolerance test. Combined therapeutic and toxic result. Heart rate slowed but ectopic beats occur.

and no extrasystoles were noted under continual observation. Without further diuretic drugs, the congestive failure improved, and the patient was able to take digitalis without fear of nausea. Further improvement ensued with re-introduction of mercurial diuresis.

Case 4. Digitalis contra-indicated. A man, aged 50 years, was admitted with advanced congestive heart failure due to coronary artery disease. Gross anasarca and gallop rhythm, and frequent attacks of cardiac asthma. B.P. 130/80. Serum potassium 4·6 m.eq. per litre. Various courses of digitalis and diuretic therapy over a period of two years. Some weeks before admission he had been taking digitalis foliata gr. i thrice daily, but his condition deteriorated. As he had persistent tachycardia in spite of digitalis treatment an acetyl strophanthidin test was carried out as a guide to further management. When 0·7 mg. acetyl strophanthidin had been injected auricular and nodal extrasystoles appeared. After one hour when a total dose of 1·7 mg. had been given, multiform ventricular extrasystoles frequently occurred, and the test was then stopped (Fig. 3). The heart rate was not significantly altered.

Interpretation. Further digitalis administration would be likely to produce toxic arrhythmias which might be fatal. Moreover, no slowing of the pulse rate was likely before these toxic effects were manifest. Consequently digitalis and diuretic administration were suspended, and the patient was given potassium chloride 5 g. orally each day in divided doses. Ten days later the patient's condition improved, and slow oral digitalization was instituted using digitalis foliata, and diuretic therapy was recommenced. The patient responded with slowing of the pulse rate and profuse diuresis and considerable clinical improvement.

Case 5. Digitalis indicated. A woman, aged 62 years, was admitted to hospital with advanced congestive heart failure due to coronary artery disease. Anasarca, gallop rhythm, and cardiac asthma. B.P. 150/80. Serum potassium 4·5 m.eq. per litre. She had a history of recurrent heart failure during the previous five years with varying courses of digitalis and diuretic therapy. Previous hospital admissions confirmed that at times she had *pulsus bigeminus* requiring interruption of digitalis treatment. One week before admission, digitalis had to be omitted on account of intense nausea and vomiting, and the occurrence of coupled beats. As she had rapid auricular fibrillation

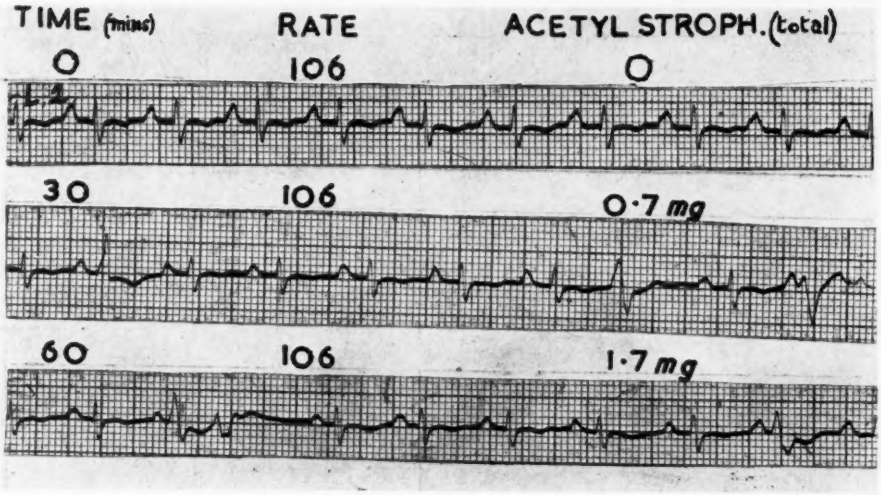


FIG. 3.—Case 4. Acetyl strophanthidin tolerance test. Toxic result. Occurrence of ectopic beats.

(rate 150 a minute) and in view of the previous history, an acetyl strophanthidin tolerance test was carried out to help determine her digitalis status. When 0·5 mg. acetyl strophanthidin had been administered the ventricular rate showed evidence of slowing, and when a total of 1 mg. had been given over a period of one hour, the auricular fibrillation was controlled (rate 60–75 a minute). No nausea or any other untoward effect was observed.

Interpretation. The slowing of the heart rate by acetyl strophanthidin appeared to indicate that complete rapid digitalization was required. As the patient was apprehensive about taking digitalis by mouth on account of nausea, digoxin was given by the intravenous route. Within 48 hours when a total of 2·5 mg. had been administered, the heart rate was 60–70 a minute. This was accompanied by considerable improvement, and it was found possible to maintain digitalization with oral digoxin without undue nausea. When diuretic therapy was recommenced, there was a satisfactory response. Four weeks later the patient was well enough to be out of bed.

Case 6. Digitalis indicated. A man, aged 59 years, was admitted with advanced congestive heart failure due to coronary artery disease (cardiac infarction four years previously). During the last two years he had recurrent episodes of congestive failure with varying courses of digitalis and diuretic therapy. He had been confined to bed for two months and was receiving 0·25 mg. digoxin twice daily and 2 ml. mersalyl twice weekly. But he failed to improve, and admission to hospital became necessary. There was rapid auricular fibrillation with frequent ventricular extrasystoles. In view of the ectopic beats, the possibility of digitalis toxicity was entertained. Consequently an acetyl strophanthidin tolerance test was carried out to determine his digitalis requirements. The results are shown in Fig. 4. Two hours later a total of 2·2 mg. of the drug had been administered, the heart rate was slowed from 95–100 to 60–75 a minute and the ventricular extrasystoles were completely abolished.

Interpretation. Digitalis was required for this patient to slow the heart rate. The extrasystoles were a manifestation of myocardial disease and not due to digitalis. Consequently oral digitalization was instituted by digoxin 0·25 mg. six-hourly with diuretic therapy. One week later the pulse rate was 80 a minute and there was considerable clinical improvement.

Case 7. Digitalis indicated. A man, aged 66 years, was admitted with advanced congestive heart failure due to chronic rheumatic heart disease. He had rapid auricular flutter. Before admission he had been receiving digoxin 0·25 mg. thrice daily by mouth and diuretic therapy for many months.

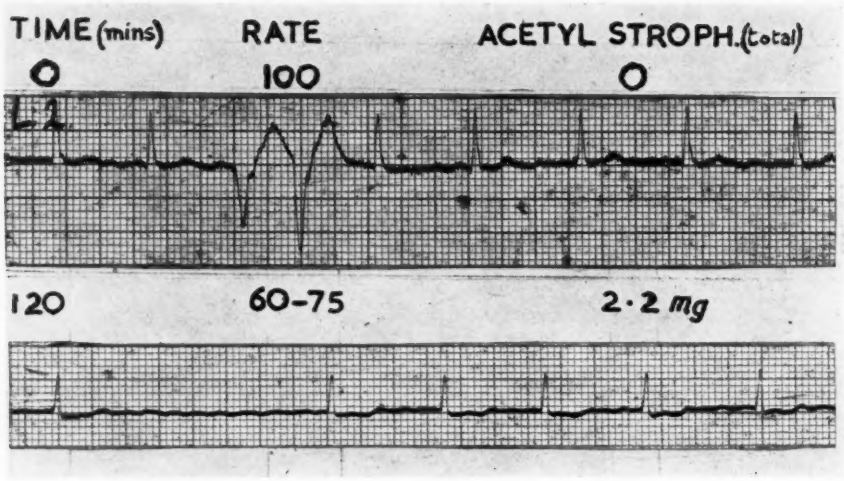


FIG. 4.—Case 6. Acetyl strophanthidin tolerance test. Therapeutic result. Heart rate slowed and ectopic beats abolished.

B.P. 150/80. Serum potassium 6·4 m.eq. per litre. He complained of nausea but nevertheless was able to tolerate oral digitalis. In view of the rapid ventricular rate, and the failure of the digitalis dosage to effect control, an acetyl strophanthidin tolerance test was carried out to determine the possible response to further digitalis administration. Fig. 5 shows the result. Four hours

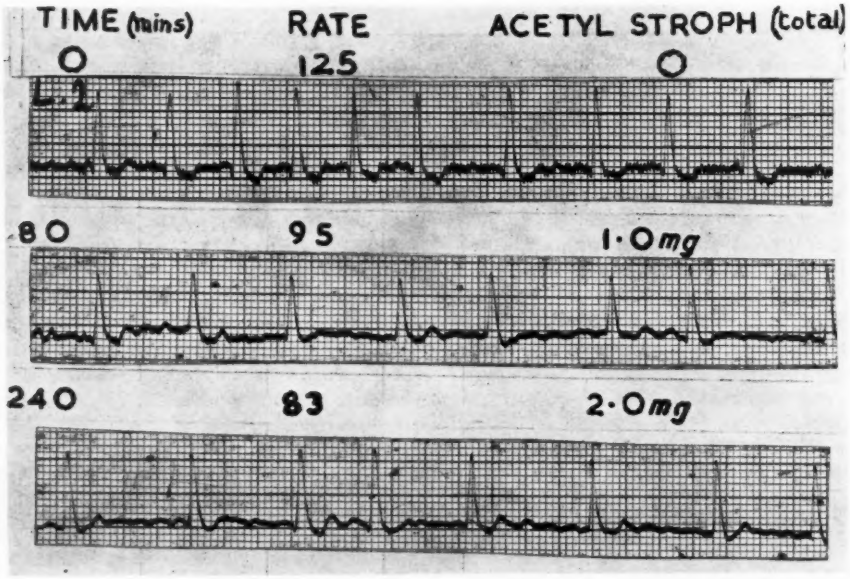


FIG. 5.—Case 7. Acetyl strophanthidin tolerance test. Therapeutic result. Heart rate slowed.

after 2 mg. of the drug had been given the heart rate had fallen from 105–140 to 80–100. No nausea or vomiting occurred during the test.

Interpretation. Digitalis was indicated to control the heart rate. The patient's nausea was due to congestive changes and not to digitalis intoxication. Consequently digitalis foliata was administered in doses of gr. i four-hourly until adequate slowing of the heart was obtained.

Case 8. Digitalis indicated. A man, aged 63 years, was admitted with congestive heart failure due to coronary artery disease. He had anasarca and pulmonary œdema. B.P. 190/115. Serum potassium 4·6 m.eq. per litre. He had received digitalis and diuretic therapy at varying times during the previous six years. For two months he had been confined to bed at home, and was receiving digitalis foliata gr. i thrice a day along with diamox therapy. However, it had to be omitted as he had nausea and vomiting and extrasystoles. In view of these factors it was decided to carry out an acetyl strophanthidin test. At the end of three hours when a total of 1·8 mg. acetyl strophanthidin had been administered, the heart rate was slowed from 130–150 to 80–90 a minute. The extrasystoles were abolished with the slowing of the heart rate. No nausea or vomiting occurred during the test.

Interpretation. Digitalis was required to slow the heart rate. The nausea and vomiting were due to local congestive changes and not to digitalis. The extrasystoles were due to the underlying heart disease and not to digitalis toxicity. Consequently digitalization was carried out using intravenous digoxin, to avoid nausea by the oral route. After 1·5 mg. digoxin had been given the pulse rate fell to 84 a minute. No extrasystoles occurred. Digitalization was maintained by oral digoxin without undue nausea.

Case 9. Combined digitalis and potassium therapy indicated. A woman, aged 63 years, was admitted to hospital with congestive heart failure due to coronary artery disease (an old posterior infarction). She had auricular fibrillation and pulmonary œdema with hydrothorax. There was a history of congestive failure of varying degree over a period of two years. No information was available about the amount of digitalis she had had prior to admission. On account of the uncontrolled auricular fibrillation 0·25 mg. digoxin was administered daily by mouth. After a few days' treatment, she developed intense nausea and vomiting. The digitalis was omitted for a few days, but when recommenced the nausea promptly recurred. Her pulse rate continued to be rapid. It was decided thereafter to carry out an acetyl strophanthidin tolerance test as a guide to her digitalis requirements. The lead selected (AVF) confirmed the presence of auricular fibrillation and posterior infarction (Fig. 6.) When only 0·4 mg. acetyl strophanthidin had been given, the heart rate significantly slowed from 125 to 95, though this was accompanied by frequent ventricular extrasystoles. No nausea occurred during the test.

Interpretation. Digitalis was indicated to slow the heart rate. However, as the slower rate was likely to be associated with extrasystoles, potassium was indicated to suppress them. Consequently the patient was digitalized with digitalis foliata gr. i. thrice daily and potassium chloride 5 g. daily was given orally. A week later the pulse rate was 70, and no extrasystoles were noted. The patient's condition was considerably improved by adequate digitalis treatment.

Discussion

All the cases were in the older age group and coronary artery disease was the prevalent underlying cause of intractable failure. It was probably also a factor in Cases 2 and 7. With an ageing population such cases are likely to increase, and any help with their management is opportune. The wide range in dosage of acetyl strophanthidin (0·4–2·2 mg.) required to produce a result indicates the difficulty of assessing adequate digitalis dosage based on clinical observation only. Moreover, it is reasonable to assume that when a therapeutic effect occurs, the amount of acetyl strophanthidin administered may be a guide to the dosage of conventional digitalis preparations required for control of the pulse rate. The clinical features of Cases 2 and 4 in which digitalis was contraindicated differed little from the remaining cases in which digitalis was urgently required. This difficulty is a characteristic feature of intractable heart failure. Perusal of the case histories in our series reveals the inadequacy of digitalis treatment prior to the acetyl strophanthidin tolerance

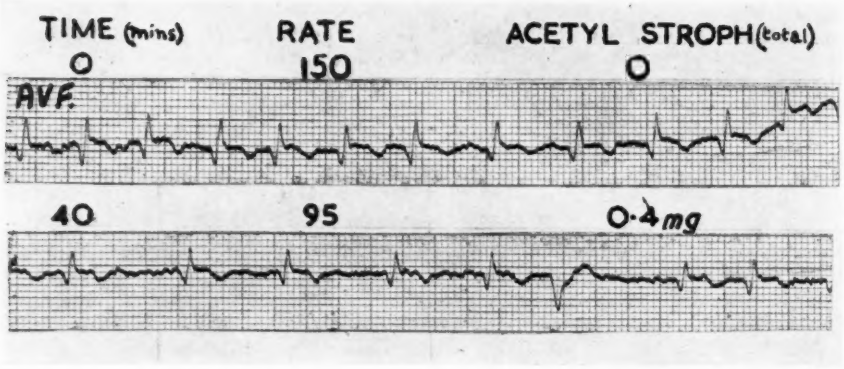


FIG. 6.—Case 9. Acetyl strophanthidin tolerance test. Combined therapeutic and toxic result. Heart rate slowed but ectopic beats occur.

test. Nausea may preclude further oral therapy. Some of our patients refused to take digitalis by mouth. Tachycardia and ectopic rhythms are responsible for varying opinions about what should be done and as a result "therapeutic half measures" are usually adopted. Digitalis may be given, then omitted, then recommenced with varying dosage. Such measures are not only undesirable but may be dangerous. The acetyl strophanthidin tolerance test represents a step away from empiricism in digitalis management in these cases, as it affords objective evidence on which treatment can be based with greater confidence.

We wish to draw attention to the qualitative difference between the therapeutic and toxic action of digitalis on the diseased heart. Whereas therapeutic action slows the heart by vagal stimulation and increasing the cardiac output, toxic action produces ectopic beats due to local effect of the drug on isolated groups of cardiac cells. This is in keeping with modern theory concerning extrasystolic impulse formation (Scherf and Schott, 1953). Our results have been interpreted on this basis. It is notoriously difficult to produce pulsus bigeminus by the pharmacological action of digitalis on the normal heart, in contra-distinction to its very frequent occurrence when the heart is diseased (Scherf and Schott, 1953). The results of our investigations appear to indicate that in the presence of heart disease there is competition between the therapeutic action of digitalis on the heart as a whole, and its toxic action on isolated groups of cardiac cells causing ectopic rhythms. In Cases 2 and 4 acetyl strophanthidin produced multiform ventricular extrasystoles without alteration in pulse rate, i.e. the toxic action was predominant. In the seven other cases it slowed the heart rate though in some instances this was accompanied by a toxic action causing ectopic beats (Cases 3 and 9). In Cases 1, 6 and 9 acetyl strophanthidin not only slowed the heart rate, but thereby abolished ventricular extrasystoles. The explanation of this paradoxical action of the drug on ectopic foci appears to be that the longer diastolic pause at slower heart rates permits more efficient coronary filling, thereby relieving myocardial anoxia which is responsible for ectopic beats when the heart rate is fast. Thus digitalis can produce a therapeutic effect, a toxic effect, or a combination of both, and this interplay between the therapeutic and toxic action explains the varying response of the diseased heart to digitalization. Our experience shows that the smaller the amount of digitalis that produces toxic arrhythmias, the more severe is the underlying cardiac disease. When digitalis produces only toxic manifestations, the final stage of myocardial breakdown has been reached.

Acetyl strophanthidin is a potent drug, and ventricular fibrillation has been reported during its use (Enselberg *et al.*, 1951). Considerable experience is required for the selection of cases suitable for a test dose. Fresh myocardial infarction should be excluded. Serial electrocardiographic

control is essential, and the observer must be competent to recognize immediately the significance of the changes in rhythm. In our series, the objective was to administer the minimal amount of the drug to produce a response. A full therapeutic or toxic effect was not necessarily produced. All our cases had tachycardia (4 auricular fibrillation, 3 sinus tachycardia, 1 auricular flutter, 1 auricular tachycardia). However, the basic rhythm must be analysed electrocardiographically to exclude toxic digitalis tachycardia such as ventricular tachycardia, and auricular tachycardia with A-V block (Heyl, 1932). Disturbance of A-V conduction is also a contra-indication to the test. Nausea and vomiting is not a contra-indication. It is important to note that six of our patients (Cases 1, 3, 5, 7, 8, 9) who had nausea as a prominent symptom did not manifest an emetic response to acetyl strophanthidin. Only one (Case 2) developed nausea and vomiting during the test. In intractable failure the nausea associated with visceral congestion seriously interferes with adequate digitalization maintenance. It cannot be differentiated from the central emetic action of digitalis except by intravenous therapeutic trial such as with acetyl strophanthidin. No subjective paræsthesiae occurred during the test in any of our patients, as noted by Lown and Levine (1955). With the technique used no necessity for procaine amide administration arose. Moreover, the risk of the test is less than the risk of administering digitalis in the presence of potential digitalis poisoning, or failing to administer the drug when it is urgently required.

Apart from intractable heart failure, the acetyl strophanthidin tolerance test may be of great value in assessing digitalis requirements when the sensitivity of the heart to digitalis has been altered by potassium loss associated with surgical operations. A digitalized patient may require adjustment of dosage following operation due to vomiting or dietetic restriction. Lown and Levine (1955) describe the use of the test after valvotomy. Thus it opens a new field in the post-operative management of cardiac patients receiving digitalis.

Certain important deductions can be made concerning digitalis treatment schedules based on the results of the acetyl strophanthidin tolerance test. Diuretic therapy is suspended until the digitalis requirement has been ascertained. If a toxic response alone occurs (Cases 2 and 4) then, of course, digitalis is omitted, and potassium administered to suppress the activity of ectopic foci. We have used oral potassium in dosage of 5 g. daily. Usually after two to five days the potassium balance is adequately restored to allow recommencement of digitalis therapy, and dosage which was previously toxic came within the therapeutic range. None of our patients suffered undue nausea from oral potassium treatment in spite of intense nausea when digitalis was given. When a therapeutic response only is obtained, then obviously, digitalis must be given (Cases 1, 5, 6, 7, 8). Important principles then arise concerning dosage and route of administration. No digitalis treatment is attempted until at least ten hours after the trial dose of acetyl strophanthidin to avoid a combined action of the drugs. Adequate oral digitalis dosage by mouth may be impossible on account of nausea and vomiting. Urgent action may be imperative and in such cases we have digitalized our patients using the intravenous route (Cases 1, 5, 8) basing the dose of digoxin on the amount of acetyl strophanthidin used for the test. We believe that this measure was life-saving in our cases, and the view that digitalis should never be given intravenously when the patient has been already taking the drug by mouth may require revision. Our view is that intravenous digitalis therapy may be urgently indicated in such cases and may be the only effective route to produce maximum benefit in a limited period of time. In Cases 3 and 9 a combined therapeutic and toxic effect occurred when acetyl strophanthidin was given. We regard this result as an indication for combined treatment with digitalis and potassium, to enable the patient to have the benefit of the therapeutic action of the drug without toxic manifestations. Potassium chloride 5 g. is given orally daily, concurrently with digitalis, usually during the first two to five days. Serial electrocardiographic study is essential when potassium is given to adjust dosage and prevent toxic effects. It should be noted that serum potassium levels are no guide to treatment. In most of our cases they were within the normal range. It is a negative potassium balance that determines increased sensitivity to digitalis, and obviously patients with intractable heart failure requiring urgent treatment are not suitable for complete metabolic study. Combined digitalis and potassium treatment in selected cases is a therapeutic

advance. The use of digitalis following fresh infarction may be associated with serious toxic arrhythmias. If it is combined with potassium administration, toxic manifestations may be suppressed, so permitting the patient to benefit from its therapeutic action. This problem is now under investigation by us.

Summary

The complex factors in relation to digitalis therapy in intractable heart failure are discussed, especially in relationship to potassium metabolism. The acetyl strophanthidin tolerance test is described and applied to nine patients. The results obtained indicate new principles of digitalis treatment based on the concept of competition between its therapeutic and toxic actions on the diseased heart. Parenteral administration of digitalis is entirely justifiable if indicated by the test dose of acetyl strophanthidin, irrespective of previous dosage of the drug, especially if nausea prevents oral treatment. Combined digitalis and potassium therapy represents a therapeutic advance in selected cases. Tachycardia may occur with serious digitalis toxicity, and in many instances the acetyl strophanthidin test alone can differentiate it from tachycardia requiring urgent digitalis treatment.

References

Berliner, R. W., Kennedy, T. J., and Orloff, J. (1951). *Amer. J. Med.*, **11**, 274.
Burrows, B. A., and Sisson, J. H. (1950). *J. Clin. Invest.*, **29**, 801.
Calhoun, J. A., and Harrison, T. R. (1931). *J. Clin. Invest.*, **10**, 139.
Chen, K. K., and Elderfield, R. C. (1942). *J. Pharmacol. exper. Therap.*, **76**, 81.
Dennis, J., and Moore, R. M. (1938). *Amer. J. Physiol.*, **123**, 443.
Eggleston, C. (1915). *Arch. intern. Med.*, **16**, 1.
Enselberg, C. D., Croce, J. P., and Lown, B. (1951). *Circulation*, **3**, 647.
Gold, H., Otto, H. L., Modell, W., and Halpern, S. L. (1943). *J. Pharmacol. exper. Therap.*, **86**, 39.
Greiner, T., and Reilly, J. (1952). *Proc. Soc. exper. Biol.*, **81**, 141.
Harvey, R. H., Ferrer, M. I., Cathcart, R. T., Richards, D. W., and Cournand, A. (1949). *Amer. J. Med.*, **7**, 439.
Hatcher, R. A., and Weiss, S. (1922). *Arch. intern. Med.*, **29**, 690.
Heyl, A. F. (1932). *Ann. intern. Med.*, **5**, 858.
Lesser, G. T., Dunning, M. F., Epstein, F. H., and Berger, E. Y. (1952). *Circulation*, **5**, 85.
Levine, H. D. (1948). *Ann. intern. Med.*, **29**, 822.
Lown, B., and Levine, S. A. (1955). *Current Concepts in Digitalis Therapy*. Churchill.
——, Salzberg, H., Enselberg, C. D., and Weston, R. E. (1951). *Proc. Soc. exper. Biol.*, **76**, 797.
Root, M. A., and Chen, K. K. (1953). *Proc. Soc. exper. Biol.* **84**, 131.
Sampson, J. J., Alberton, E. C., and Kondo, B. (1943). *Amer. Heart J.*, **26**, 164.
Scherf, D., and Schott, A. (1953). *Extrasystoles and Allied Arrhythmias*. Heinemann.

The acetyl strophanthidin for these investigations was supplied by The Medical Research Department, Eli Lilly & Co., Indianapolis.

THE VECTORCARDIOGRAM IN ATRIAL SEPTAL DEFECT

BY

NEIL A. J. HAMER

The Institute of Cardiology and the National Heart Hospital

Received June 19, 1957

The right ventricular hypertrophy in uncomplicated atrial septal defect results from an increase in stroke output. The electrocardiogram in these circumstances differs from that when there is a raised right ventricular pressure (Cabrera and Monroy, 1952). The right bundle-branch-block pattern is frequent, and was found in 95 per cent of the patients with uncomplicated atrial septal defect studied by Barber *et al.* (1950). Vectorcardiography shows that the RSR′ in lead V1 in these cases is produced by moderate right ventricular hypertrophy (Lasser *et al.*, 1951) (Fig. 1).

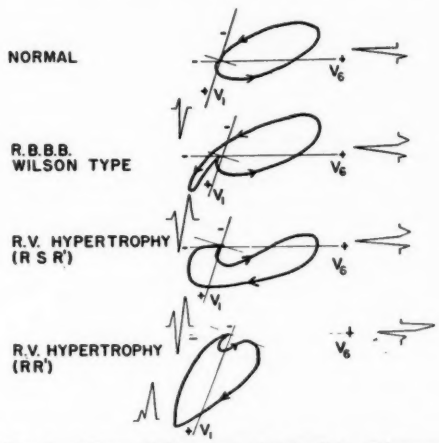


FIG. 1.—(From Grishman and Scherlis). Diagrams of the horizontal projection of the QRS loop of the vectorcardiogram with the derived præcordial ECC leads V1 and V6. In the normal subject and in R.B.B.B. the loop is counte r-clockwise in sense, while in both types of R.V· hypertrophy it is clockwise. An RSR′ pattern is lead V1 is found in both R.B.B.B. and R.V. hypertrophy, though the vectorcardiograms differ considerably.

A series of patients with atrial septal defect were studied to see if there were any distinctive features of the vectorcardiogram in right ventricular hypertrophy with an increased stroke output. Evidence of additional left ventricular hypertrophy was also sought. This may be due to a ventricular septal defect or to mitral incompetence, indicating that the atrial septal defect is part of a defect of the atrio-ventricular cushions. Present techniques do not allow safe repair of this type of defect, so detection before operation is important.

Material and Methods

Forty patients were studied. The presence of an atrial septal defect was established by cardiac catheterization in all, and was confirmed in 12 at subsequent operation. Cases with pulmonary hypertension or pulmonary stenosis were excluded.

Cardiac Catheterization. The technique followed was that described by Wood (1956). The pulmonary blood flow was expressed as a ratio to the systemic flow. In calculating these flows it was assumed that the oxygen saturation of the superior vena caval sample was representative of the whole venous return, and that the pulmonary venous blood was 95 per cent saturated.

The presence of a left-to-right shunt at ventricular as well as atrial level, with the passage of the catheter to the left ventricle and aorta without sharp angulation, was regarded as evidence of an atrio-ventricular cushion defect.

Electrocardiography. A Cambridge photographic machine was used. The electrocardiograms were classified from the appearance in lead V1 which showed an RSR′, RR′, or QR pattern in most cases. Complete right bundle-branch block was diagnosed when the QRS complex was 0·12 sec. wide or more. If the QRS complex was narrower than this, but showed a secondary R wave in lead V1, it was classified as incomplete right bundle-branch block.

In the absence of bundle-branch block, right ventricular hypertrophy was diagnosed when R in V1 was 7 mm. or more in height (Sokolow and Lyon, 1949). An R′ of 10 mm. or more was taken to indicate right ventricular hypertrophy in addition to right bundle-branch block when the QRS width was between 0·10 and 0·12 sec. (Barker and Valencia, 1949). In complete bundle-branch block, additional right ventricular hypertrophy was diagnosed when R′ was 15 mm. or more (Booth *et al.*, 1956).

Vectorcardiography. The apparatus described by Dower and Moore (1955) was used. The lead system was that recommended by Grishman *et al.* (1951): four electrodes are placed on the thorax at the corners of an imaginary cube, and are connected to give three bipolar leads with a common electrode on the right lower back. The leads are combined in pairs, one on each axis of the oscilloscope, to produce vectorcardiograms in the horizontal, frontal, and sagittal planes, which are recorded photographically.

The Einthoven system of polarity was used, in which directions are indicated from the point of view of the subject. Forces directed forwards, downwards, or to the left are regarded as positive.

The oscilloscope beam was interrupted 80 times per second. The rate of inscription of the vectorcardiogram is indicated by the distance between these interruptions. As each break is abrupt, and the next segment has a pointed origin, the direction of inscription is easily detected.

Results

Atrial Septal Defect. In 35 patients there was no evidence of an atrio-ventricular cushion defect. The only complications present were anomalous pulmonary venous drainage (4), mitral stenosis (2), pulmonary regurgitation (1), and tricuspid regurgitation (1). These complications tend to increase the stroke output of the right ventricle.

The electrocardiogram showed complete right bundle-branch block in 18 with right ventricular hypertrophy in 1, incomplete right bundle-branch block in 16 with right ventricular hypertrophy in 5, and was normal in 1 patient. Atrial fibrillation was present in 5 patients.

The pulmonary blood flow varied from 1·4 to 6·7 times the systemic flow. The pulmonary vascular resistance was less than 3 units (240 dynes sec. cm.$^{-5}$) and the arterial oxygen saturation more than 90 per cent in every case. Some patients had a systolic pressure gradient at the pulmonary valve, but this was never more than 20 mm. Hg.

The vectorcardiograms of these patients were classified as follows:

Right ventricular hypertrophy	24
Right ventricular hypertrophy with R.B.B.B.	1
Normal with some delay in R.V. activation	8
Normal	2

In 24 patients the vectorcardiogram showed right ventricular hypertrophy (Fig. 2). The QRS vector was directed anteriorly and inferiorly forming a clockwise loop in the horizontal plane but remaining close to the transverse axis. A small initial deflection representing septal activation was usually present. The remainder of the loop consisted of a narrow left deflection followed by a

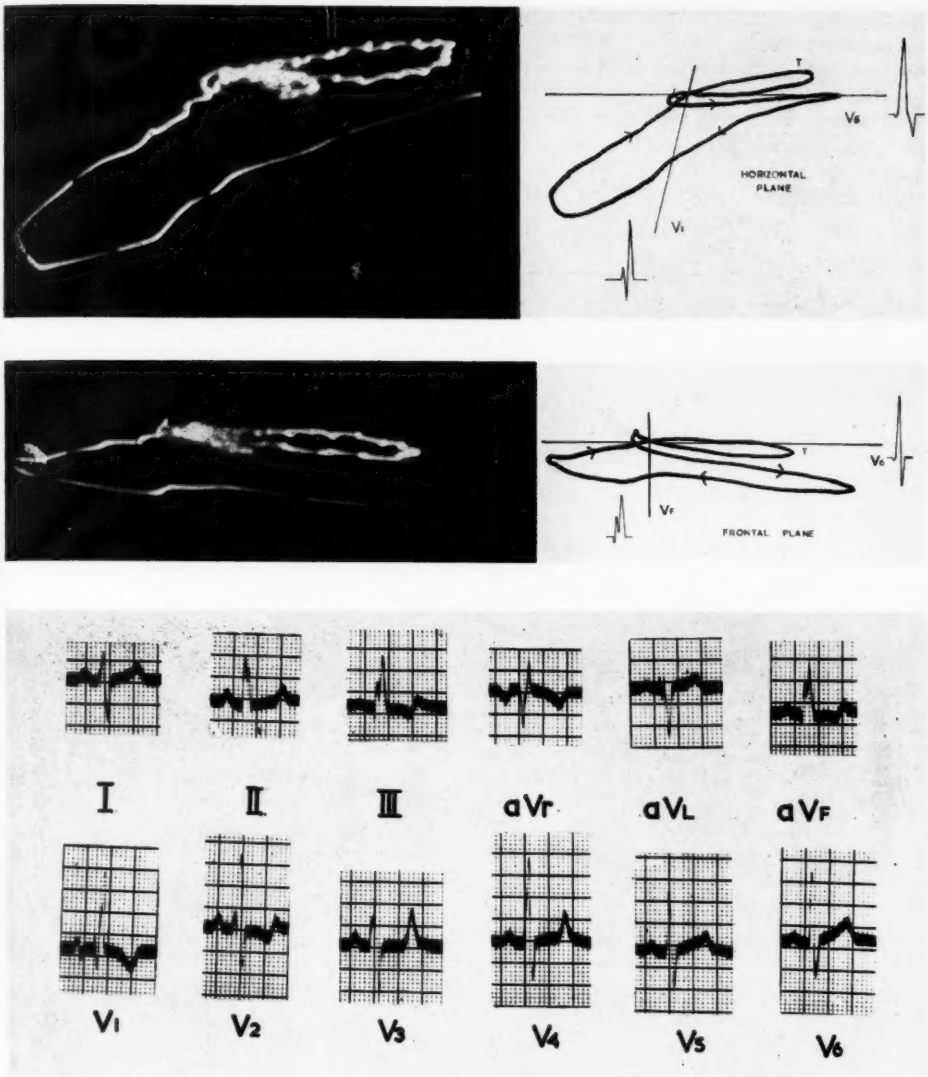
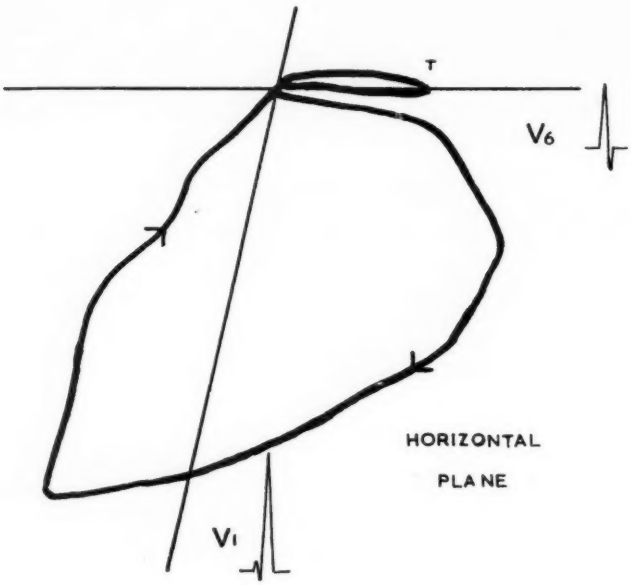


FIG. 2.—The vectorcardiogram and electrocardiogram in a patient with atrial septal defect, showing right ventricular hypertrophy of moderate degree. Diagrams of the horizontal and frontal projections of the vectorcardiogram are shown alongside the corresponding photographic records. In the diagrams the axial leads V1, V6, and aVF are shown. The QRS loop is narrow, and the vector remains close to the transverse axis.

wider right deflection with slowing of part of the returning limb. In three patients the slow segment involved some of the outgoing limb also. The T loop was directed to the left. The variations in the vectorcardiogram within this group could not be correlated with the pulmonary blood flow.

18 patients with pulmonary hypertension or stenosis were studied for comparison. In 6

with high right ventricular pressures, the QRS vector passed further forwards and downwards than in atrial septal defect, to form a more circular loop (Fig. 3). The 9 subjects with moderate right ventricular hypertension had QRS loops similar to those found in atrial septal defect. However, 13 of the patients with atrial septal defect had narrower QRS loops than any in the group with a raised right ventricular pressure. Three patients with mild pulmonary stenosis had normal vectorcardiograms.



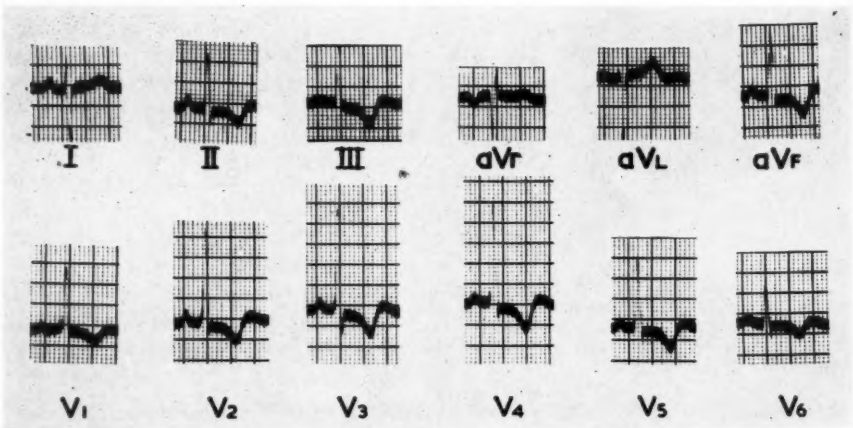
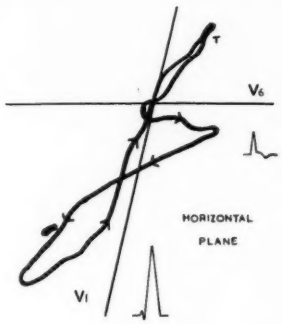


FIG. 3.—Diagram of the vectorcardiogram in the horizontal plane and the electrocardiogram in a patient with severe pulmonary stenosis, showing right ventricular hypertrophy of severe degree. The QRS loop is nearly circular in this plane.

One patient with atrial septal defect had tricuspid regurgitation. The right deflection of the QRS loop was more anterior than usual in this case, and was counterclockwise in the horizontal plane (Fig. 4). The T loop was directed posteriorly. This pattern indicates right bundle-branch block in addition to right ventricular hypertrophy.

In 8 patients with atrial septal defect the QRS loop was close to the transverse axis, as in the group showing right ventricular hypertrophy, but differed in sense. The left deflection was counterclockwise in the horizontal plane as in normal subjects. The right deflection varied, and the outgoing and returning limbs often crossed (Fig. 5). The electrocardiogram and the findings at cardiac catheterization were in no way unusual in these patients.



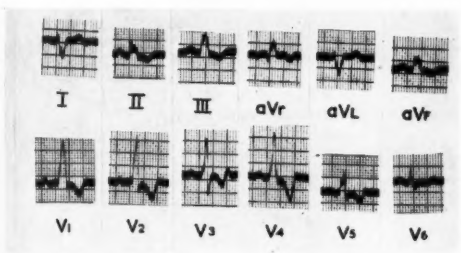
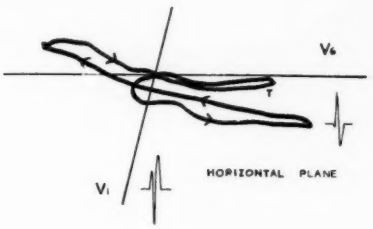


FIG. 4.—Diagram of the vectorcardiogram in the horizontal plane and the electrocardiogram in a patient with R.V. hypertrophy and R.B.B.B. The clockwise initial part of the loop indicates R.V. hypertrophy, while the late anterior counterclockwise component indicates R.B.B.B. This pattern was found in only one patient with atrial septal defect.



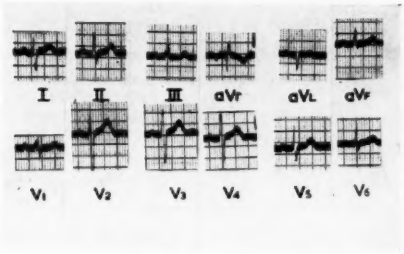


FIG. 5.—Diagram of the vectorcardiogram in the horizontal plane and the electrocardiogram in a patient with atrial septal defect, showing a counterclockwise left deflection. The later right deflection is clockwise in sense. This pattern was interpreted as normal L.V. dominance with some delay in R.V. activation.

A normal vectorcardiogram was found in two subjects with atrial septal defect. One had a normal electrocardiogram, but in the other patient an embryonic R′ was present in lead V1.

Artio-ventricular Cushion Defect. There was evidence of an atrio-ventricular cushion defect in 5 patients (Table). In four mitral incompetence was detected clinically. The electrocardiogram showed left ventricular hypertrophy in two (R in V6 32 and 28 mm.), and the P–R interval was prolonged in the 4 patients with sinus rhythm.

The vectorcardiograms fall into three groups. In two subjects the pattern was similar to that found in atrial septal defect. The other three showed left axis deviation in the electrocardiogram. This was reflected in the vectorcardiogram as a QRS loop directed superiorly (Fig. 6). There was an unusual degree of terminal slowing of the loop in two patients.

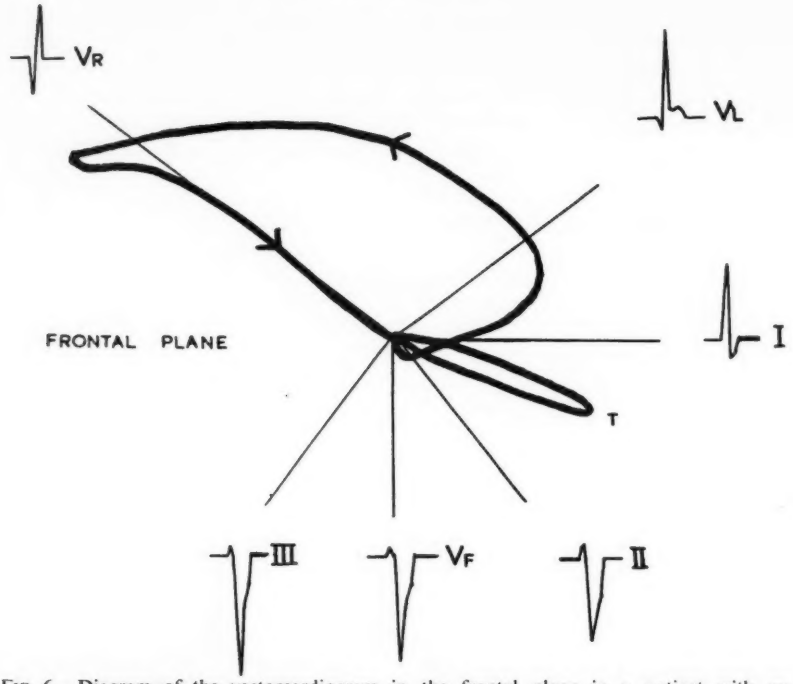


FIG. 6.—Diagram of the vectorcardiogram in the frontal plane in a patient with an atrio-ventricular cushion defect. The standard and unipolar limb leads with their corresponding axes are shown in the diagram. The QRS loop is directed superiorly, and the electrocardiogram shows left axis deviation in the standard leads.

TABLE

ATRIO-VENTRICULAR CUSHION DEFECTS

Sex	Age	Clinical evidence of mitral regurgitation	Evidence of A-V cushion defect at catheterization	Electrocardiogram			Vectorcardiogram		
				P–R interval	L.A.D.	QRS pattern	Right anterior appendix	Unusual terminal slowing	Ventricular dominance
♀	28	+	O	0·26	O	RBBB inc.	O	O	Right
♂	59	+	O	AF	O	RBBB	O	O	Right
♂	18	+	+	0·24	++	RBBB +LVH	O	O	Combined
♀	39	O	+	0·21	++	RBBB	O	+	Combined
♂	27	+	O	0·28	+	RBBB +LVH	+	+	Left

Cardiac catheterization showed evidence of an atrio-ventricular cushion defect in two subjects. In both the QRS loop in the horizontal plane had a counterclockwise left deflection indicating left ventricular dominance. This was followed by a clockwise right deflection interpreted as evidence of right ventricular hypertrophy (Fig. 7). The remaining patient had a similar counterclockwise left deflection which continued into a right anterior terminal appendix indicating right bundle-branch block.

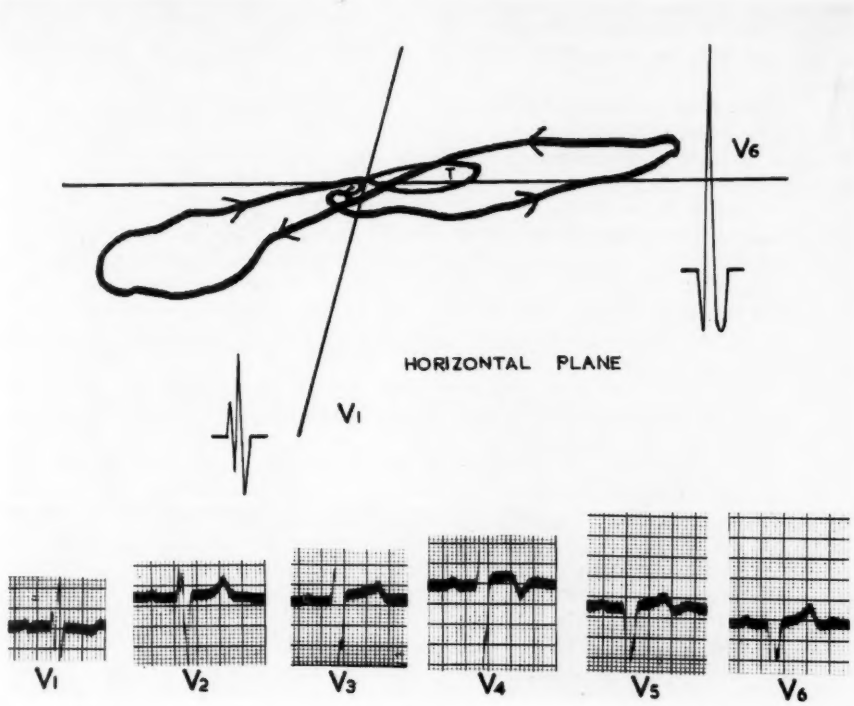


FIG. 7.—Diagram of the vectorcardiogram in the horizontal plane and the electrocardiogram in a patient with an atrio-ventricular cushion defect. The counterclockwise left deflection indicates L.V. dominance, but the later clockwise right deflection suggests some R.V. hypertrophy.

DISCUSSION

Right bundle-branch block in normal subjects or ischæmic heart disease produces a characteristic vectorcardiogram. The QRS loop has a terminal appendix directed anteriorly and to the right (Lasser *et al.*, 1951) (Fig. 1). Braunwald *et al.* (1956) found that the onset of right ventricular systole was delayed in subjects showing this pattern. The right anterior appendix may therefore be regarded as definite evidence of right bundle-branch block. It was found in two patients in the present series.

Braunwald *et al.* (1956) also found delay in right ventricular systole in some subjects with lesions producing right ventricular hypertrophy. The vectorcardiogram in these patients shows an unusual degree of terminal slowing of the QRS loop. In 9 atrial septal defects with this slowing reported by Silverblatt *et al.* (1957) the QRS loop was directed superiorly. An upwardly directed QRS loop in atrial septal defect suggests a defect of the atrioventricular cushions. The terminal slowing may represent a modification of the right bundle-branch block vector in the presence of left ventricular hypertrophy. Two patients in this series showed unusual terminal slowing of an upwardly directed QRS loop, but in both there was other evidence of left ventricular hypertrophy (Fig. 7).

The vectorcardiogram in the 24 patients showing right ventricular hypertrophy is similar to that described by Richman and Wolff (1955) and Silverblatt *et al.* (1957) in atrial septal defect. Wolff *et al.* (1953) regard the right deflection of the QRS loop in these cases as evidence of impaired conduction in the hypertrophied right ventricle. The T loop axis is directed away from these late

QRS forces as it is in right bundle-branch block. The unusual degree of terminal slowing found in some subjects may also indicate defective conduction. The delay in activation must be confined to part of the right ventricle as the onset of mechanical systole is normal in this group (Braunwald *et al.*, 1956).

The narrow QRS loop probably reflects the distribution of the right ventricular muscle in atrial septal defect. The ventricle is dilated to accommodate the increased stroke output, and the hypertrophy is mainly evident in the muscle bands of the crista supraventricularis and the trabeculæ (Kjellberg *et al.*, 1955). The thick free wall of right ventricular hypertension is not found, so no large anterior forces are produced by right ventricular activation. The late right deflection may arise from the region of the crista supraventricularis (Walker *et al.*, 1956).

A normal left deflection of the QRS loop was found in 8 patients. The right ventricular forces have failed to overcome the normal dominance of the left ventricle in these cases. The right deflection shows a similar conduction disturbance to that found in the group with right ventricular hypertrophy. This abnormality of conduction is not a constant feature of atrial septal defect as it was absent in the two patients with normal vectorcardiograms.

Five patients showed features suggesting *atrio-ventricular cushion defect*. The left ventricular hypertrophy in two was apparently not sufficient to affect the vectorcardiogram. In the remaining three the QRS loop was directed upwards. This is probably the result of left ventricular hypertrophy, which is also evident as a counterclockwise left deflection in the horizontal plane. Toscano-Barbosa *et al.* (1956), however, suggest that there is a specific abnormality of conduction in this condition, as this vectorcardiographic pattern is found in patients with the ostium-primum type of defect without mitral incompetence or ventricular septal defect. These authors report 16 patients with atrio-ventricular cushion defects and classify the vectorcardiograms in three groups, each with a characteristic frontal QRS axis. One consists of cases with pulmonary hypertension which were excluded from this series. Two of the present cases fall in the group with balanced ventricular hypertrophy, and the other shows left ventricular dominance.

A prolonged P–R interval is a frequent finding (Milnor and Bertrand, 1957).

Conclusions

Of 35 patients with uncomplicated atrial septal defect, 25 had vectorcardiograms showing moderate right ventricular hypertrophy with some impairment of conduction. 13 of these had a narrower QRS loop than any found in a series of patients with pulmonary hypertension or stenosis. Three subjects showed unusual terminal slowing of the loop. In 10 patients the vectorcardiogram did not show right ventricular hypertrophy, but in 8 of these there was evidence of a conduction disturbance in the right ventricle. In all, 22 patients with atrial septal defect showed distinctive vectorcardiographic features.

The vectorcardiogram is helpful in differential diagnosis, as it does not show right ventricular hypertrophy in normal subjects with right bundle-branch block or in mild pulmonary stenosis. These may be confused with atrial septal defect clinically.

Three of the five patients in whom an atrio-ventricular cushion defect was suspected showed characteristic vectorcardiograms that can be recognized in the electrocardiogram as left axis deviation.

Vector analysis is helpful in revealing the fundamental changes in the electrocardiogram in atrial septal defect, but many problems of interpretation remain.

The apparatus used was constructed by Dr. M. K. Towers, First Assistant to the Academic Unit, the Institute of Cardiology. I wish to thank Dr. D. Evan Bedford, Dr. Paul Wood, and Dr. Wallace Brigden for much encouragement and advice, and the physicians of the National Heart Hospital for permission to study patients under their care; also Mrs. Olive Connolly of the Photographic Department of the Institute for her help with the illustrations.

Fig. 1 is reproduced from *Spatial Vectorcardiography* by A. Grishman, and L. Scherlis, (1952) by permission of the publisher, W. B. Saunders Company.

References

Barber, J. M., Magidson, O., and Wood, P. (1950). *Brit. Heart J.*, **12**, 277.
Barker, J. M., and Valencia, F. (1949). *Amer. Heart J.*, **38**, 376.
Booth, R. W., Chou, T.-C., and Scott, R. C. (1956). *Circulation*, **14**, 914.
Braunwald, E., Donoso, E., Sapin, S. O., and Grishman, A. (1956). *Circulation*, **13**, 866.
Cabrera, E. C., and Monroy, J. R. (1952). *Amer. Heart J.*, **43**, 669.
Dower, G. E., and Moore, A. D. (1955). *Amer. Heart J.*, **49**, 705.
Grishman, A., Borun, E. R., and Jaffe, H. L. (1951). *Amer. Heart J.*, **41**, 483.
Kjellberg, S. R., Mannheimer, E., Rudhe, U., and Jonsson, B. (1955). *Diagnosis of Congenital Heart Disease:* p. 66.
Lasser, R. P., Borun, E. R., and Grishman, A. (1951), *Amer. Heart J.*, **41**, 667.
Milnor, W. R., and Bertrand, C. A. (1957). *Amer. J. Med.*, **22**, 223.
Richman, J. L., and Wolff, L. (1955). *Amer. Heart J.*, **50**, 85.
Silverblatt, M. L., Rosenfeld, I., Grishman, A., and Donoso, E. (1957). *Amer. Heart J.*, **53**, 380.
Sokolow, M., and Lyon, T. P. (1949). *Amer. Heart J.*, **38**, 273.
Toscano-Barbosa, E., Brandenburg, R. O., and Burchell, H. B. (1956). *Proc. Staff Meetings Mayo Clinic*, **31**, 513.
Walker, W. J., Mattingly, T. W., Pollock, B. E., Carmichael, D. B., Inmon, T. W., and Forrester, R. H. (1956). *Amer. Heart J.*, **52**, 547.
Wolff, L., Richman, J. L., and Soffe, A. M. (1953). *New Eng. J. Med.*, **248**, 851.
Wood, P. (1956). *Diseases of the Heart and Circulation:* 2nd ed., p. 179.

NORADRENALINE SENSITIVITY IN HYPERTENSION MEASURED WITH A RADIOACTIVE SODIUM TECHNIQUE

BY

R. MOULTON, A. G. SPENCER, AND D. A. WILLOUGHBY

From the Medical Unit, University College Hospital Medical School

Received July 8, 1957

There have been reports of an increased sensitivity to adrenaline or noradrenaline of the blood vessels of patients with hypertension (Greisman, 1952; Lee and Holze, 1951). In an attempt to test such abnormal sensitivity preliminary observatons were made with intradermal injections of noradrenaline in normal and hypertensive subjects. Intradermal noradrenaline (0·1 μg.) gave an area of blanching which slowly faded, and the duration of the blanching was considerably increased in the hypertensive patients. However, the end point was indefinite and it was difficult to express the result quantitatively. A technique was therefore developed in which the rate of disappearance of radioactive sodium from muscle was measured before and after local injections of noradrenaline. Noradrenaline was chosen rather than adrenaline because it is now generally agreed that noradrenaline is liberated at sympathetic nerve endings. The results obtained have been correlated with the blood pressure of the subjects.

METHODS

The rate of disappearance of radioactive sodium (^{24}Na) from muscle was measured using the technique first described by Kety (1948, 1949) and reviewed by McGirr (1952). The method was modified by leaving the needle used for injecting ^{24}Na *in situ*. After an initial ^{24}Na clearance had been determined noradrenaline or saline was injected through the needle, and a further set of readings was taken from which the ^{24}Na clearance was calculated.

The following standard procedure was adopted. Observations were made at the bedside on subjects who had been resting in bed for at least 30 minutes. Exposure was reduced to the minimum. 0·2 ml. of isotonic saline containing ^{24}Na with an activity of 2–5 μC. was injected from the front into the quadriceps muscle about the mid-point of the thigh. This was washed in with 0·1 ml. of saline and the needle was left *in situ*. A screened gamma ray Geiger-Muller counter was placed along the side of the thigh and wedged in position. The subject was asked not to move the limb. The counting rates were recorded at half-minute intervals during the observation period using a direct reading counting rate meter. After three minutes equilibration a set of 20 readings was taken. 0·2 ml. of noradrenaline solution in saline (0·5 μg/ml. noradrenaline bitartrate, plus 5 mg./ml. ascorbic acid and 5 mg./ml. sodium metabisulphite as preservatives) was then injected through the same needle. This amount of noradrenaline was chosen as preliminary observations showed that this was the minimum amount regularly to produce a slight decrease in the clearance of ^{24}Na from the muscle of normal subjects. In control experiments the noradrenaline was replaced by saline containing the preservatives. After another three minutes equilibration a further set of readings was taken. Since the same size needle (Serum V) was used on each occasion the dead space was the same. The noradrenaline and control saline solutions were made up in ampoules and sterilized by steaming for 15 minutes. The noradrenaline content was checked weekly on the cat's blood pressure preparation. The needle prick caused only trivial discomfort. As the duration of the experiment was short, corrections for the decay of ^{24}Na and for the rising background due to recirculation of ^{24}Na were negligible and have not been made. When the counts were plotted against time the points fell, as expected, about an exponential curve, and by plotting log counts against time the points fell about a straight line. The equation of the line was calculated by the method of least squares and the slope obtained. From this the time taken for the counts to fall to half value ($T\frac{1}{2}$) was calculated, being log $\frac{1}{2}$ times the reciprocal of the slope of the line.

The time to half value after noradrenaline was calculated in the same way and the difference between the two values attributed to the effect of noradrenaline.

A diastolic blood pressure of 90 mm. of mercury or more was taken arbitrarily to indicate hypertension. The age and sex distributions of subjects in the groups with normal and raised blood pressures were comparable.

RESULTS

The results of a typical observation are shown in Fig. 1. Fig. 2 is a diagram showing the kind of result obtained in subjects with normal and with raised pressures, and also the effect of replacing noradrenaline by the control saline solution. Noradrenaline decreased the rate of disappearance of ^{24}Na in all subjects and hence prolonged the time to half value. The results obtained from 13 observations on 10 subjects with normal pressure and from 28 in 20 hypertensive patients are summarized in the Table.

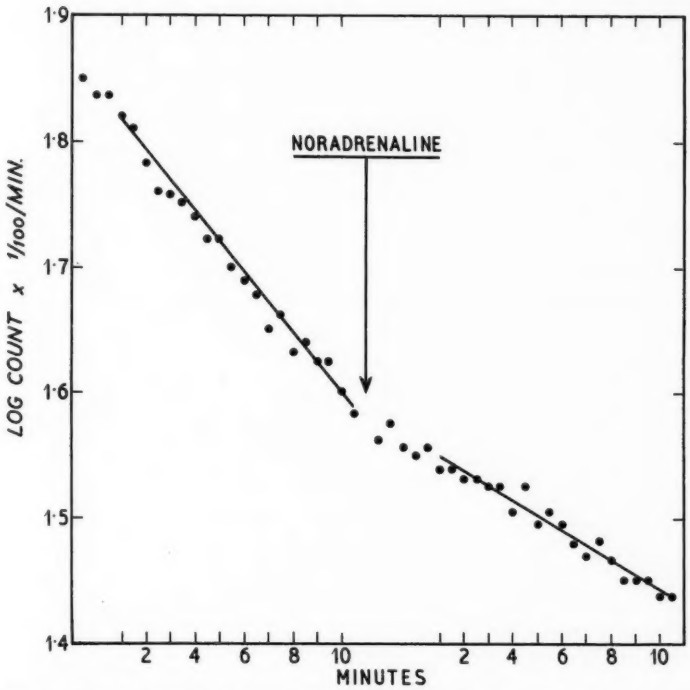


FIG. 1.—The effect of 0·05 μg of noradrenaline on the clearance of ^{24}Na from human quadriceps muscle.

The mean clearance rates of ^{24}Na in these groups did not differ significantly before noradrenaline, nor was there any difference in the mean clearances of the groups with normal and with raised pressures after noradrenaline. However, the mean change in time to half value after the injection of noradrenaline was significantly greater ($p \leqslant 0{\cdot}001$) in the hypertensive subjects, the mean increase being 13·9 min. and for the normals 6·3 min. This was true of both the absolute change in times to half value after noradrenaline and also of the change expressed as percentages of either initial or final times to half value. Thus the hypertensive subjects showed a greater change following noradrenaline than did the subjects with normal blood pressure.

The agreement between results of repeat observations on the same patient was poor, and was

TABLE

SUMMARY OF THE RESULTS AND THE STATISTICAL TESTS APPLIED TO THE DATA

			I	II	II–I	$\frac{II-I}{I}\times 100$	$\frac{II-I}{II}\times 100$
	Blood pressure (mm. Hg)		Initial time to half value (min.)	Time to half value after noradrenaline (min.)	Change in time to half value (min.)	Percentage change in time to half value	Percentage change in time to half value
	Systolic	Diastolic					
Mean of 13 observations on 10 subjects with normal pressure ..	129·6	68·5	21·8	28·15	6·3	32·4	21·5
Standard deviation ..	14·7	13·0	9·8	11·0	5·0	30·3	14·5
Mean of 28 observations on 20 hypertensive subjects	183·4	118·6	18·4	32·3	13·9	78·1	41·2
Standard deviation ..	29·3	17·0	5·8	12·0	8·7	41·7	12·7
Difference of means			3·4	4·15	7·6	45·7	19·7
Test of difference			1·2	1·2	4·3	4·6	4·6
Significance level			N.S.	N.S.	0·001	0·001	0·001
Correlation coefficient with diastolic blood pressure			−0·17	+0·21	+0·44	+0·39	+0·63
Significance level			N.S.	N.S.	0·01	0·01	0·001
Correlation coefficient with systolic blood pressure			−0·19	+0·11	+0·32	+0·50	+0·51
Significance level			N.S.	N.S.	0·05	0·001	0·001

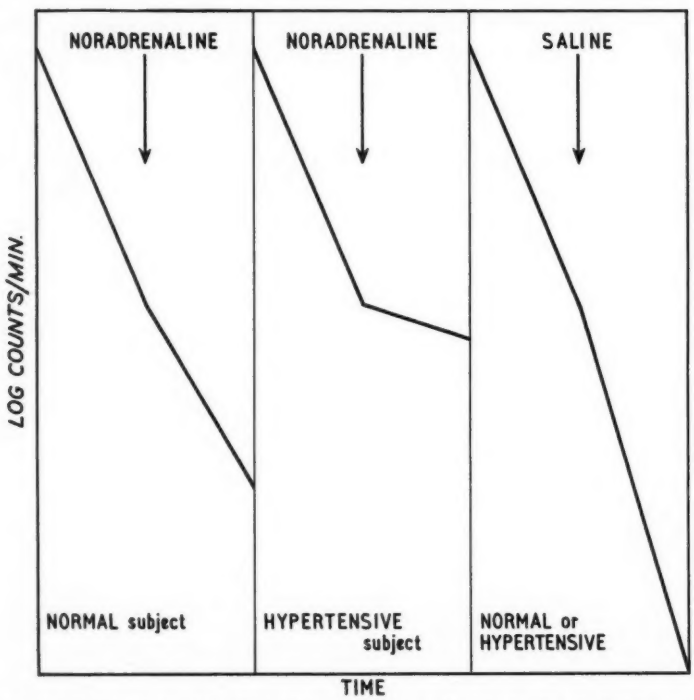


FIG. 2.—Diagram showing effect of noradrenaline and control saline on the clearance of ^{24}Na from the muscle of subjects with normal pressure and with hypertension.

worse when they were done on different days. Although our subjects have arbitrarily been divided into those with normal and those with a raised blood pressure, the level of the pressure is a continuous variable (Hamilton *et al.*, 1954). Fig. 3 shows the difference between the times to half value (expressed as a percentage) before and after noradrenaline or saline, plotted against diastolic blood pressure. When the absolute change in time to half value is used as the ordinate or the systolic blood pressure as the abscissa similar graphs are obtained. These graphs all show a high degree of positive correlation between response to noradrenaline and the level of the blood pressure. The comparison of means and the correlation coefficients are given in the Table. Repeat observations on the same subject have been included, but the significance is not altered by taking only the first result. The significance was tested using the tables of Fisher and Yates (1953).

When noradrenaline was replaced by control injections of saline there was an increased clearance of ^{24}Na in 8 out of 9 observations (Fig. 3). The mean decrease in time to half value after injection of saline was 4·4 min. (S.D. 4·7 min.).

$\frac{II-I}{II} \times 100$
Percentage change in time to half value
21·5
14·5
41·2
12·7
19·7
4·6
0·001
+0·63
0·001
+0·51
0·001

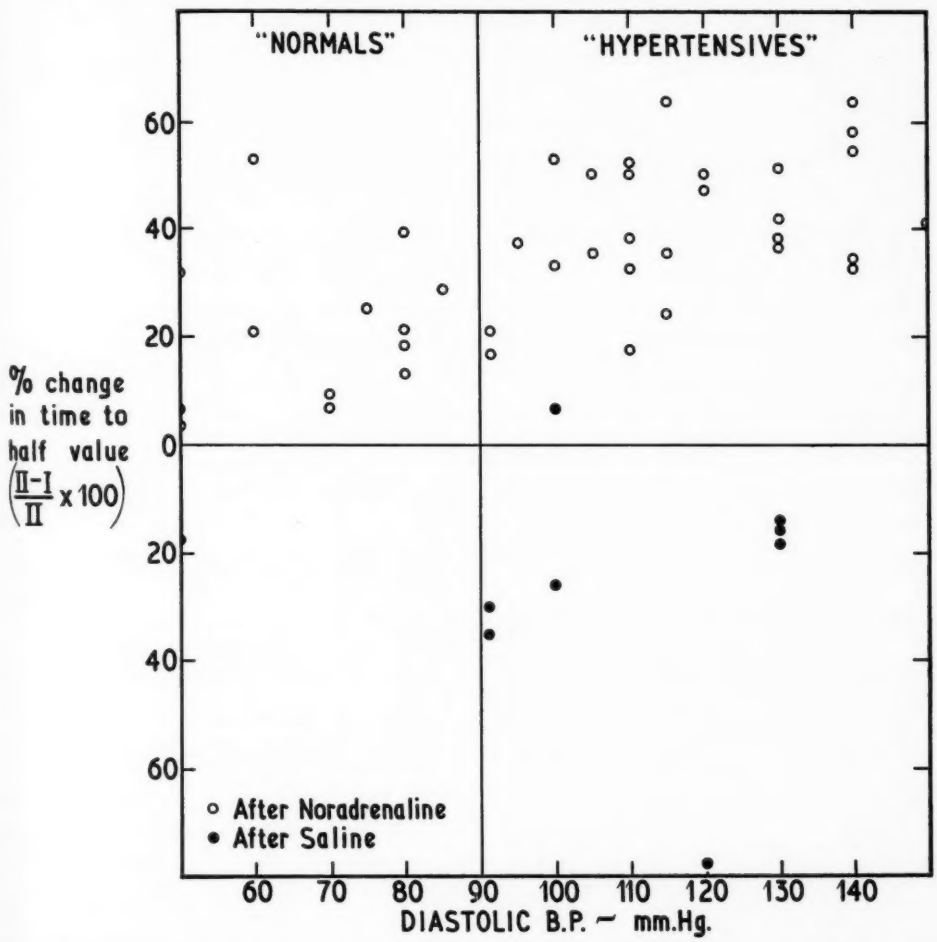


FIG. 3.—The percentage change in time to half value after noradrenaline or saline, and the diastolic blood pressure.

The response to noradrenaline in renal or essential hypertension was found to be related only to the level of blood pressure and not to the cause of the hypertension.

Discussion

In these observations the ^{24}Na clearance has been used to measure the response to injected noradrenaline. The ^{24}Na clearance rates are probably the resultant of many different factors but we are concerned only with the change following local noradrenaline injections. Walder (1955) has shown that, within wide limits, a change in ^{24}Na clearance closely parallels a change in muscle blood flow. In this study, as expected, there was no correlation between the initial ^{24}Na clearance and the blood pressure. Even in severe peripheral vascular disease resting ^{24}Na clearances may not be altered (Cooper *et al.*, 1949). The variation between different determinations in the same patient is in agreement with the results of others (Wisham *et al.*, 1951; Reese *et al.*, 1951; McGirr, 1952). Although the method does not give very reproducible results in the individual patient, statistically an increased sensitivity to noradrenaline has been found in the present group of hypertensive subjects.

The effect of intravenous infusions of noradrenaline on the blood pressure was investigated by Goldenberg *et al.* (1948), who found that hypertensive subjects gave a larger response than controls to the same dose. Judson *et al.* (1950) were not able to confirm this and considered that the percentage rise in the earlier workers' results did not differ from that of controls. Greisman (1952) has shown that the capillaries in the nail-bed are abnormally sensitive to noradrenaline in hypertension, and Lee and Holze (1951) using adrenaline, obtained comparable results by examining the conjunctival vessels. Using a plethysmographic technique, Duff (1956, 1957) has recently shown an increased response to intra-arterial injections of adrenaline in most hypertensive subjects, this effect being greatest in those most severely affected. The effect of noradrenaline was very much less than that of adrenaline.

These results, obtained by several workers using a variety of techniques and working on different vascular beds, seem to indicate an increased response of the peripheral vessels in hypertension to local pressor amines. This could result either from an increased sensitivity of the smooth muscle in the vessel wall, or from an impairment of the local mechanism which normally destroys or removes pressor amines.

Summary

An increased sensitivity to intramuscular noradrenaline in hypertensive patients has been demonstrated using a ^{24}Na clearance technique.

We are grateful to Professor M. L. Rosenheim for encouragement and advice, to Mr. S. B. Osborne and Dr. H. S. Payling Wright for helpful discussions, to Mr. N. W. Please for help with the statistics, and to Mr. V. K. Asta for the Figures.

References

Cooper, F. W., Jr., Elkin, D. C., Shea, P. C., Jr., and Dennis, E. W. (1949). *Surg. Gynec. Obstet.*, **88**, 711.
Duff, R. (1956). *Hypotensive Drugs*. Ed. M. Harington, Pergamon Press, London.
—— (1957). *Brit. Heart J.*, **19**, 45.
Fisher, R. A., and Yates, F. (1953). *Statistical Tables for Biological, Agricultural and Medical Research*. Oliver and Boyd Ltd., Edinburgh.
Goldenberg, M., Pines, K. L., Baldwin, E. F., Greene, D. G., and Roh, C. E. (1948). *Amer. J. Med.*, **5**, 792.
Greisman, S. E. (1952). *J. clin. Invest.*, **31**, 782.
Hamilton, M., Pickering, G. W., Fraser Roberts, J. A., and Sowry, G. S. C. (1954). *Clin. Sci.*, **13**, 11.
Judson, W. E., Epstein, F. H., and Wilkins, R. W. (1950). *J. clin. Invest.*, **29**, 1414.
Kety, S. S. (1948). *Amer. J. med. Sci.*, **215**, 352.
—— (1949). *Amer. Heart J.*, **38**, 321.
Lee, R. E., and Holze, E. A. (1951). *J. clin. Invest.*, **30**, 539.
McGirr, E. M. (1952). *Brit. med. Bull.*, **8**, 192.
—— (1952). *Clin. Sci.*, **11**, 91.
Reese, H. L., Darrow, R. P., and Cullen, M. L. (1951). *Surg. Gynec. Obstet.*, **92**, 751.
Walder, D. N. (1955). *Clin. Sci.*, **14**, 303.
Wisham, L. H., Yalow, R. S., and Freund, A. J. (1951). *Amer. Heart J.*, **41**, 810.

SIMPLE METHOD FOR ESTIMATING MITRAL REGURGITATION BY DYE DILUTION CURVES

BY

JOHN SHILLINGFORD*

From the Department of Medicine, Postgraduate Medical School of London

Received December 2, 1957

Stewart (1894), Kinsman *et al.* (1929), and Hamilton *et al.* (1932, 1948) first showed it possible to estimate cardiac output from a mathematical analysis of dilution curves produced by the passage of an indicator substance through the circulation; good agreement was found between the cardiac output obtained by this and by the direct Fick method. They suggested that the volume between the point of injection and the site of sampling could be calculated from the product of the cardiac output and mean circulation time. More recently we have shown that for a given calculated output and volume the spread of the indicator particles in the curve is fixed within narrow limits (Korner and Shillingford, 1955, 1956). The addition of valvular incompetence in the passage of the indicator substance increases the spread of the particles quite apart from the effect of cardiac output or volume

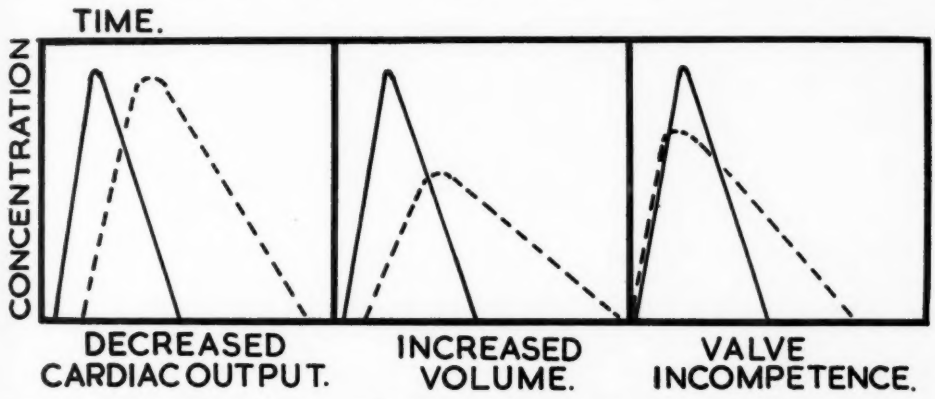


FIG. 1.—Time concentration dilution curves plotted semi-logarithmically to show the effect of cardiac output, volume through which the indicator passes, and valvular incompetence. (The unbroken line represents the reference curve in each case.)

(Fig. 1) and this increase may be used to give an indication of the regurgitant flow through an incompetent valve. We have previously described a method for estimating backflow involving double regression equations (Korner and Shillingford, 1955, 1956). The purpose of this paper is to describe a simple empirical method for obtaining an index of regurgitation from dye curves without involved mathematical calculation.

* Member Scientific Staff, Medical Research Council.

METHOD

Evans blue dye (T–1820), 10–20 mg. in 1 to 2 ml. normal saline, was rapidly injected into the pulmonary artery or right atrium through a cardiac catheter; pulmonary arterial injection gives the total regurgitant flow through the mitral and aortic valves, and right atrial injection the total through all the cardiac valves. The passage of dye through the ear was recorded by a photo-electric cell earpiece and recorder* based on the design of Wood and Geraci (1949). All patients breathed a high concentration of oxygen from a polythene mask for five minutes before and during the time of recording the dye dilution curves to maintain the blood at constant oxygen saturation.

The spread of the particles in the curve was measured arbitrarily by plotting the curve on semi-logarithmic paper in the normal way used for calculating cardiac output by the Hamilton method and measuring the width of the curve in seconds at a height of one-tenth the maximum concentration (Fig. 2). This figure was divided by the appearance time in seconds to give the ratio of the spread to the appearance time.

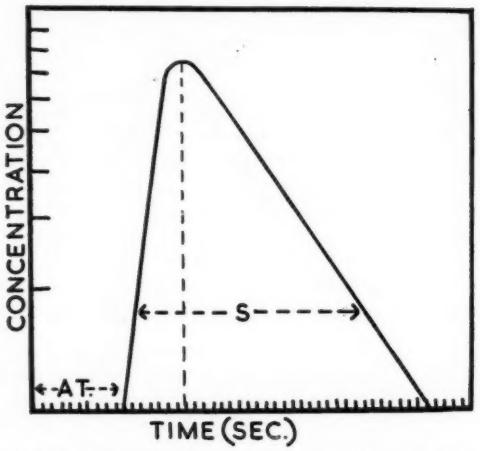


FIG. 2.—The measurements used to determine appearance-time/spread ratio. AT = appearance time in seconds. S = spread of curve in seconds at arbitrary figure of one-tenth the maximum concentration (drawn on logarithmic scale).

56 patients, 35 of whom had mitral valve disease with varying amounts of valvular regurgitation, were studied at the time of routine cardiac catheterization. The clinical assessment of the amount of regurgitant flow was based on auscultation of the mitral sounds and systolic murmur, left ventricular size, the pulmonary capillary pressure, and the findings at operation and necropsy. These clinical observations have been found to correspond reasonably well with the regurgitant flow estimated by the variance method previously described and are to be published in full. For the purposes of this paper the patients have been divided into those judged on clinical grounds to have no mitral regurgitation, and those with slight, moderate, and great regurgitation. Where tricuspid and pulmonary regurgitation were clinically absent the dye was injected into the right atrium, but, if they were present, into the pulmonary artery.

RESULTS

The relationship between the spread/appearance-time ratio in all the patients studied is shown in Fig. 3: it varies between 1·5 and 2·9 in 21 patients without valvular disease. This group includes patients with cardiac outputs varying from 4 to 12 litres a minute and "cardio-pulmonary" volumes from 1·1 to 4·1 litres. In 15 patients with mitral valve disease but judged to have no regurgitation,

* A suitable photo-electric recording instrument can be obtained from Messrs. Cambridge Instruments Company Ltd., Cambridge, England.

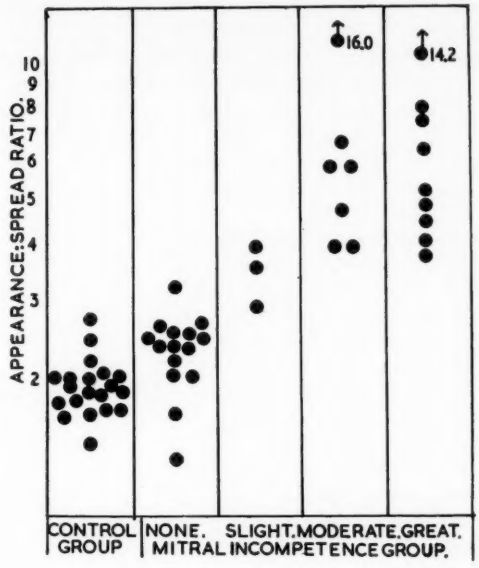


FIG. 3.—The relation between appearance-time/spread of the dye dilution curve and the clinical assessment of mitral regurgitation.

the ratio was within the same limits with the exception of one case where it was 3·2. The figure shows that with increasing valvular regurgitation the ratio becomes greater, and in the severe cases may reach as high as 16·0. In no case where regurgitation was judged to be absent was the ratio over 3·2, and where it was moderate and great the ratio was always over 4·0.

FIG. 4 shows the appearance-time/spread ratio plotted against the regurgitant flow expressed as a percentage of total left ventricular output calculated by the variance method as previously published (Korner and Shillingford, 1956) in the 35 patients with mitral valve disease; as the percentage of regurgitant flow rises the appearance/spread ratio becomes greater.

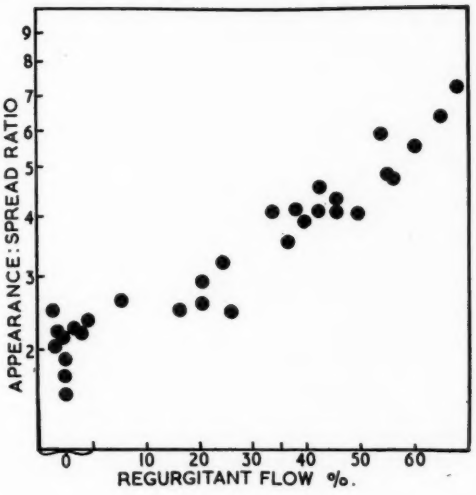


FIG. 4.—Relation between appearance-time/spread ratio and regurgitant flow expressed as a percentage of total left ventricular output calculated by the variance method.

Discussion

The validity of this method of estimating backflow depends firstly on the fact that normally the spread of the dye particles increases with the appearance time, so that in the absence of regurgitation at a valve the appearance-time/spread ratio remains relatively constant. Secondly, as we have previously shown (Korner and Shillingford, 1955, 1956), the addition of regurgitation shortens the appearance time and increases the spread of dye particles for any given calculated cardiac output and volume. It seems that this change of appearance-time/spread ratio due to regurgitation is of such a magnitude as to be useful in practice, in gaining additional information on the amount of regurgitation flow in the assessment of patients with mitral regurgitation. If the ratio is 3·0 or under significant regurgitant flow is probably not present, while over 4·0 the regurgitant flow is moderate or greater. With a ratio larger than 6·0 great regurgitation is probably present. Overlap occurs between the groups but any comparison is complicated by the difficulty of clinical and surgical assessment; allowing for this there is a progressive increase of the appearance-time/spread ratio as the estimated backflow increases.

The method has the advantage of great simplicity. Dye can be injected at the time of catheterization and a dilution curve made by the ear recorder. There is no necessity to draw a blood sample and the only calculations needed are to redraw the curve on semi-logarithmic paper and make two measurements that give the appearance-time/spread ratio.

The accuracy and value of this empirical test can only be established by practical experience in a large number of patients. On the basis of this small series it would appear to give reasonable results in mitral valve disease and to enable the absence or presence of significant mitral regurgitation to be established.

It must be emphasized, as we have stated before (Korner and Shillingford, 1955), that it is improbable that dye curves will detect slight amounts of regurgitation. There is also considerable overlap between the groups. In our experience we are finding the method a useful extra test to supplement and confirm the clinical and hæmodynamic findings in assessing patients with mitral valve disease. Like most tests in clinical medicine it must be used in association with other findings and its limits of error recognized.

Summary

A simple method for estimating valve regurgitation from dye dilution curves is described.

In a series of patients with mitral valve disease the method has separated those who clinically and surgically had no or slight regurgitation and those with moderate or great regurgitation. The practical value and the limits of error of the test are discussed.

I should like to thank Professor McMichael for his continued help and encouragement, and Dr. Hoffman and Dr. Zoob for their assistance.

References

Hamilton, W. F., Moore, J. W., Kinsman, J. M., and Spurling, R. G. (1932). *Amer. J. Physiol.*, **99,** 534.
——, Riley, R. L., Attyah, A. M., Cournand, A., Fowell, D. M., Himmelstein, A., Noble, R. P., Remington, J. W., Richards, D. W., Wheeler, N. C., and Whitham, C. (1948). *Amer. J. Physiol.*, **153,** 309.
Kinsman, J. M., Moore, J. W., and Hamilton, W. F. (1929). *Amer. J. Physiol.*, **89,** 322.
Korner, P. I., and Shillingford, J. P. (1955). *Clin. Sci.*, **14,** 553.
——, (1956). *Clin. Sci.*, **15,** 417.
Stewart, G. N. (1894). *J. Physiol.*, **15,** 31.
Wood. E. H., and Geraci, J. E. (1949). *J. Lab. clin. Med.*, **34**, 387.

CIRCULATORY EFFECTS OF CHANGING POSITION IN MITRAL DISEASE

BY

DAVID CARDUS*, JOHN MACKINNON, AND GEOFFREY WADE

From the University Department of Cardiology, Manchester Royal Infirmary

Received July 18, 1957

In a previous paper (Wade *et al.*, 1956) it was suggested that hexamethonium bromide, in lowering the raised pulmonary vascular resistance present in some cases of mitral disease, acted indirectly through changes in, or redistribution of, the blood content of the lungs; and that evidence for participation of the autonomic system was inconclusive. These views were supported by Storstein and Tveten (1954) but were at variance with those of Fowler *et al.* (1950), Meriel *et al.* (1953), Davies *et al.* (1954), and Scott *et al.* (1955), all of whom considered that the effects of ganglion-blocking drugs could only be construed as meaning that the increased hindrance was neurogenically maintained through the medium of the sympathetic system. It is necessary, therefore, to try and separate these two factors and attempt to ascertain the effects of each independently. There is a general measure of agreement that the lung blood volume is less in the erect position than in recumbency (Lagerlof *et al.*, 1951; Gilmore *et al.*, 1952; and Sjostrand, 1953), while, at the same time there is an increased systemic resistance (McMichael and Sharpey-Schafer, 1944; Stead *et al.*, 1945) and systemic vasoconstriction (Brigden *et al.*, 1950). Providing that other parameters remained relatively constant, tilting therefore appeared to offer a simple means of investigating the effects on pulmonary dynamics of altering the lung blood volume without blocking sympathetic nerve impulses.

In this paper we report the effects of tilting from recumbency to 40° feet down on pulmonary and systemic dynamics in 18 cases of mitral valve disease. We find that, whereas there is no appreciable change in pulse rate, systemic blood pressure, pulmonary ventilation, oxygen coefficient, oxygen consumption, and respiratory quotient, the pulmonary pressures are always diminished and the pulmonary vascular resistance frequently falls. The cardiac output response is somewhat variable but the peripheral resistance usually rises.

Material and Method. The material consisted of 18 patients with mitral stenosis, selected at random from those who had attended the Department of Cardiology at the Manchester Royal Infirmary for consideration of surgical treatment. Three patients (Cases 4, 7 and 11) were pregnant. All were examined in the usual manner and then subjected to cardiac catheterization, 3 grains of seconal and 0·5 g. of procaine amide being given one hour before hand. Pressures were recorded electrically by means of capacitance manometers. Systemic pressures were measured through a Cournand needle placed in the brachial artery. Mean pressures were obtained by electrical damping. Blood gases were analysed on the Van Slyke-Neill apparatus; expired air was collected in a Tissot spirometer and analysed on the Haldane apparatus.

In fifteen observations the initial measurements were made with the subject horizontal and the head resting on two pillows. After recording pressures and estimating cardiac output the table was tilted so that the patient was lying feet-down at an angle of 40° to the horizontal. This degree of tilt was chosen for the following reasons; it was an angle at which the subjects could still remain comfortably relaxed, zero-point reference errors were minimized (see below), and large gravitational effects upon the lungs were avoided. Ten to fifteen minutes after assuming this position the various measurements were repeated and the cardiac output again estimated. The subjects were then returned to the horizontal and, in eight cases the pulmonary

*British Council Post-Graduate Fellow.

arterial pressure was repeatedly recorded over the ensuing ten minutes. In two observations the subjects were unable to lie flat so the initial and final measurements were made in a 50° feet-down position while in another the order of events was reversed, the initial measurement being made at 40°. In sixteen cases the "wedge" or "pulmonary capillary venous" pressure (PCV) was recorded in both positions. In five cases, on a subsequent occasion, the intra-thoracic pressure was measured, under identical conditions, using the method of Dornhorst and Leathart (1952).

Resistances were expressed in c.g.s. units and calculated as follows:

$$\text{Total Pulmonary Resistance} = (PA_m - 5) \times 1332/\text{C.O. in ml./sec.}$$
$$\text{Pulmonary Vascular Resistance} = (PA_m - PCV) \times 1332/\text{C.O. in ml./sec.}$$
$$\text{Systemic Resistance} = BA_m \times 1332/\text{C.O. in ml./sec.}$$

where PA_m is the mean pulmonary arterial pressure, BA_m is the mean systemic pressure, PCV is the mean pulmonary venous pressure and C.O. is the cardiac output.

Ventricular work was calculated as pressure work only and expressed in kg./metres from the formulæ:

$$\text{Right Ventricular Work} = (PA_m - RA_m) \times \text{Cardiac Index} \times 0{\cdot}014$$
$$\text{Left Ventricular Work} = (BA_m - 5) \times \text{Cardiac Index} \times 0{\cdot}014.$$

The right atrial pressure was usually available, but if not it was assumed to be 4 mm. Hg in calculating right ventricular work. The mitral valve area was calculated, from the data obtained in the two positions, by the method of Gorlin and Gorlin (1951).

The Zero Reference Point. In this laboratory we have previously referred all intra-pulmonary pressures to a point 5 cm. below the sternal notch. This was chosen as it approximates to the position of the right atrium when the subject is lying down. It is, however, an unsatisfactory reference in tilting experiments for it alters in relation to both the right atrium and the lung root. We therefore decided to refer pressures to the lung root, levelling the manometer to the surface marking of the lung root, namely the mid-axillary line in the forth intercostal space. It must be appreciated that, even with this reference point, there will still be a systematic error in recording the PCV. This is because the PCV was invariably recorded in the same place, the right lower lobe. Thus with the patient tilted the catheter tip was lying below the lung root to a varying extent while when horizontal it would be lying approximately in the same plane. This error would not occur in measuring the pulmonary arterial pressure for the catheter tip was always lying at the origin of the right main branch and thus at the level of the lung root. The tendency, then, will be to record, on tilting, PCV pressures that are a little lower than the correct pressure, but this error will be trivial for the vertical distance between lung root and catheter tip with a 40° tilt is not more than 2 or 3 cm. of water, i.e. 1 or 2 mm. Hg.

Results

The pulse rate rose on tilting in ten observations, fell in two, and was unchanged in the remainder. The change was usually slight and the difference in the mean rates in the two positions was only three beats a minute.

Changes in pulmonary ventilation were inconstant and small, the mean change being a slight but insignificant rise from 4·4 to 4·5 l./min./m.^{2}. The ventilatory coefficient showed very little change, having an average of 2·77 in recumbency and 2·82 tilted. The respiratory quotient was generally almost unaltered, the mean values being 0·84 and 0·85.

There were small and inconstant changes in oxygen consumption, the mean value in the two positions being identical at 158 ml./m.^{2}. Cardiac outputs, and consequently cardiac indices, were reduced to some extent in twelve observations, the greatest drop being in the two cases in which the dynamics were most nearly normal (16 and 17): in the others the output either rose slightly or remained unchanged. The mean values were 4·29 l./min. recumbent and 3·87 l./min. at 40°, the indices being 2·74 and 2·48 l./min./m.^{2} respectively. In some cases the change in output was more dependent on alteration in arterio-venous difference rather than oxygen consumption but in others it was the converse. There was, on average, a small but insignificant increase in the arterio-venous O_2 difference from 6·45 at 180° to 6·7 ml. per 10 ml. when tilted. This is in part due to a drop in oxygen content of the pulmonary arterial blood but it is also due, in part, to a rise in brachial arterial oxygen content. This increase is oxygen saturation of the brachial arterial blood occurred in 15 of 17 observations and the difference between the mean values of 91·7 per cent and 93·3 per cent is significant.

The pulmonary arterial and pulmonary capillary pressures invariably fell on tilting, the PA systolic pressures being always affected more than the diastolic. With the exception of Cases 16 and 17 in which the dynamics were virtually normal, and Case 18 in which the pulmonary vascular resistance was extremely high, the mean arterial pressure fell more than the PCV pressure so that the PA–PCV gradient was narrowed (Fig. 1 and 2). The average fall in PA_m was from 45 to 32 mm. Hg and in the PCV from 23 to 16 mm.: both these changes are significant. In addition to a change in PCV

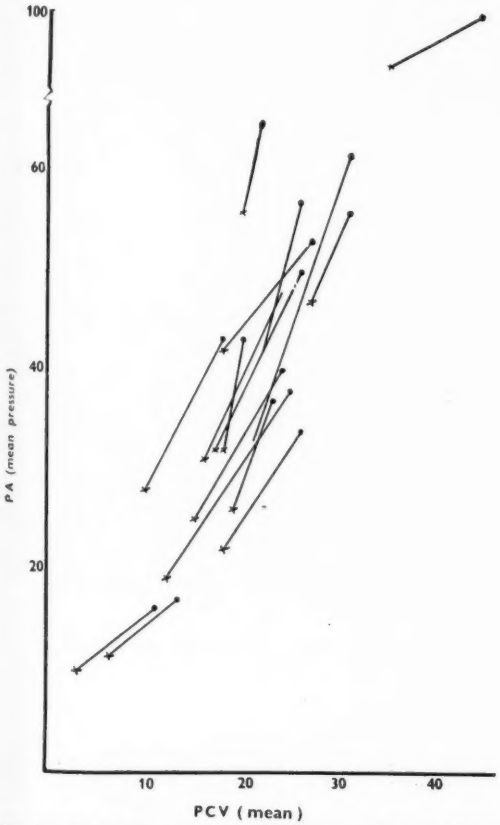


FIG. 1.—The changes in mean pulmonary arterial and PCV pressures on tilting. In this, and all subsequent figures, closed circles represent data obtained horizontal, and crosses when tilted 40° feet down from the horizontal. Pressures are expressed in mm. Hg and resistances in c.g.s. units.

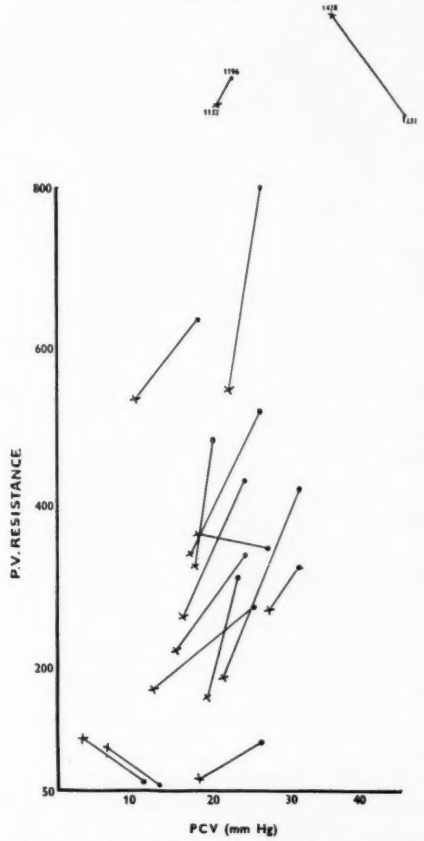


FIG. 2.—The relation between changes in PCV pressure and pulmonary vascular resistance.
One case is incorrectly shown as PVR 270→170 and PCV 25→12. The correct figure should be 150→24 and 29→12 respectively.

pressure there was also, in seven observations, a change in the form of the PCV curve. These were curves that initially possessed definitive waves. In six the major wave was late systolic and this invariably diminished in amplitude by approximately half. An example of this is shown in Fig. 3. In another there was a large early systolic wave and this also diminished in size. In the other cases the initial curve did not possess definitive waves and none appeared after tilting.

The total pulmonary resistance always fell on tilting; the extent of the fall varied with an average drop from 894 to 644 units. The pulmonary vascular resistance was calculated in 16 observations,

and it fell in 12 and rose in 4. Two in which it rose were Cases 16 and 17, in which pulmonary dynamics were normal, and a third was Case 18, in which the initial resistance was the extremely high figure of 1213 units. The largest falls were seen in those with moderately raised vascular resistances (300 to 800 units) and only one of these failed to show a fall (Case 4) (Fig. 4). In some the drop in pulmonary vascular resistance was the main cause of the fall in total resistance but in others the "non-vascular" resistance was the more important. The vascular resistance generally

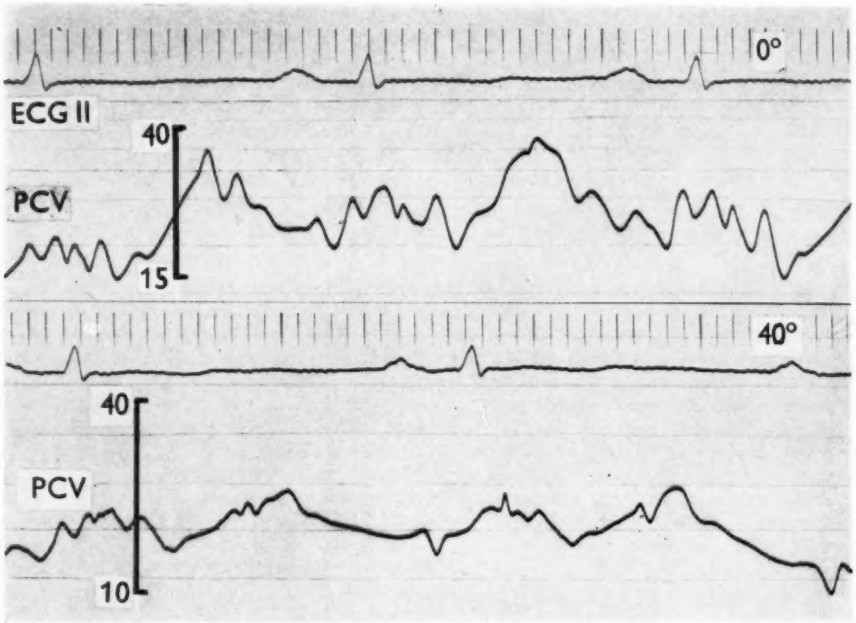


FIG. 3.—Changes in the form of the PCV pressure curve on tilting. The upper trace is with the subject horizontal. Note, below, the diminished amplitude of the late systolic wave in addition to the fall in mean pressure.

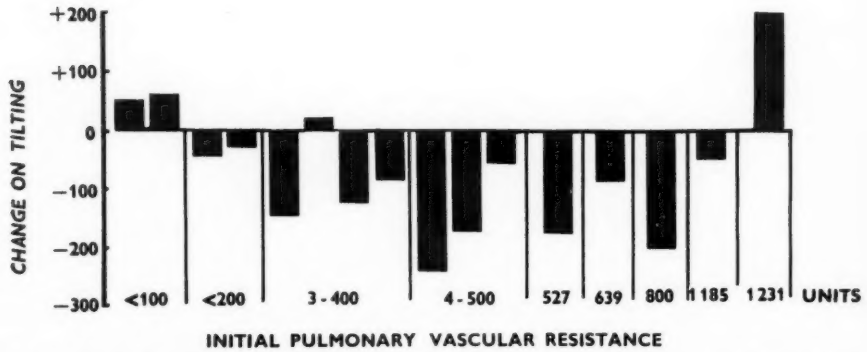


FIG. 4.—Changes in pulmonary vascular resistance in relation to the initial resistance. The changes are expressed in c.g.s. units.

followed the directional change of the PCV (Fig. 2) but failed to show this relation in the two that were hæmodynamically normal (Cases 16 and 17) and the one with an extremely high resistance (Case 18). It was less closely linked with cardiac output (Fig. 5).

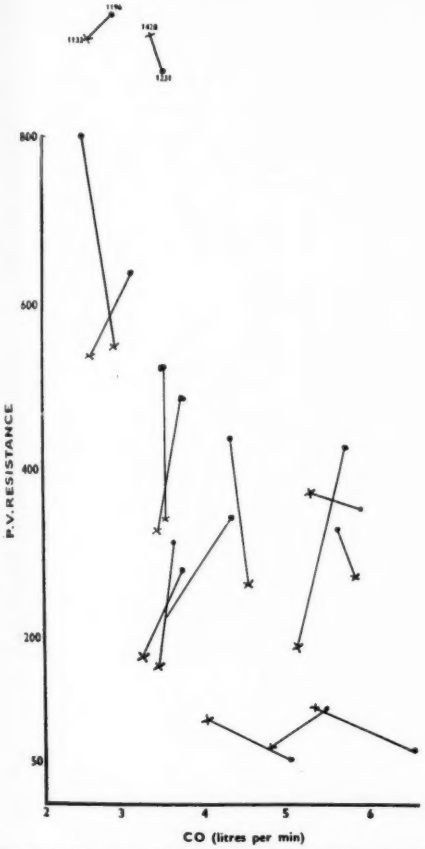


FIG. 5.—The relation between changes in PV resistance and cardiac output.

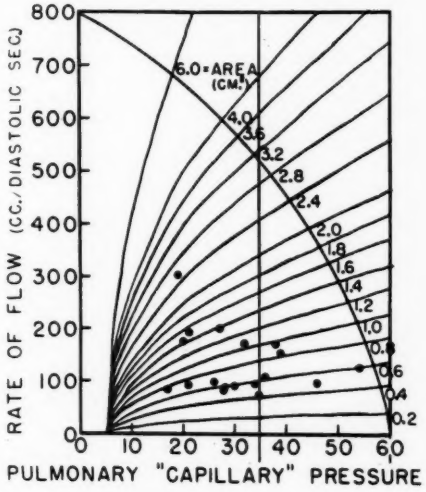


FIG. 6.—The relation between pressure and flow at the mitral valve in differing degrees of stenosis. (Reproduced by kind permission of Dr. Richard Gorlin and the C. V. Mosby Co. from the paper by Gorlin and Gorlin. 1951).

The systemic pressure changed slightly and inconsistently, the average mean reading being identical in the two positions. Peripheral resistances rose slightly in 13 of 16 observations, the average mean figures being 1546 and 1705 units recumbent and tilted; this difference is not significant.

The ventricular work invariably diminished on tilting, but whereas the left ventricular work fell by an average of only 10 per cent, a change that is hardly significant, the right ventricular work dropped by 38 per cent, a highly significant change. The mitral valve area was calculated in the two positions in ten experiments; with the exception of Case 17 the results were usually fairly close, the tilted figure being slightly larger in seven. In Case 17 the two figures were 1·47 and 2·81 cm.^{2} but this patient was judged clinically to have slight mitral regurgitation as well as stenosis and this

TABLE

CHANGES OBSERVED IN CASES OF MITRAL DISEASE,

Case No.	Position	Pulse rate	Pulmonary artery (P.A.) pressures			PCV mean pressures	Brachial artery (B.A.) pressures			Ventilation l./min./m.^{2}	Ventilation O_2 cons. l./100 ml.	R.Q.
			S	D	M		S	D	M			
1	H	100	110	54	75	—	102	58	73	3·70	3·31	0·81
	T40°	102	87	40	56	—	98	62	66	3·84	3·11	0·80
2	H	95	65	30	43	24	99	60	82	4·36	2·80	0·84
	T40°	101	38	21	25	15	114	78	90	4·56	2·75	0·86
3	H	96	100	98	65	22	115	79	89	5·46	3·30	0·83
	T40°	84	89	34	56	20	119	81	89	5·0	3·47	0·86
4	H	120	83	31	53	27	108	63	76	6·41	3·01	0·83
	T40°	120	64	27	42	18	110	71	82	5·46	3·22	0·90
5	H	100	56	28	36	29	112	60	78	4·14	2·43	0·85
	T40°	100	39	12	17	12	124	48	80	3·82	2·38	0·78
6	H	82	64	28	40	20	—	—	—	6·46	3·75	1·05
	T40°	86	55	25	34	18	—	—	—	6·81	3·87	1·10
7	H	90	79	42	56	31	116	50	66	5·32	3·04	0·86
	T40°	93	71	33	47	27	100	62	76	5·67	3·01	0·84
8	H	63	58	27	36	22	124	70	85	4·49	3·03	0·85
	T40°	63	42	18	26	19	132	74	91	4·31	2·83	0·79
9	H	120	70	32	43	18	96	78	84	5·15	3·21	0·88
	T40°	124	46	22	28	10	93	70	46	5·10	3·23	0·85
10	H	90	70	34	47·5	24	92	53	65	3·64	2·48	0·85
	T40°	90	40	21	31	16	90	55	65	4·55	2·65	0·84
11	H	90	90	42	61·5	31	104	56·5	75	5·03	2·82	0·79
	T40°	96	52	24	33	21	106	60	75	5·31	2·95	0·79
12	H	84	60	25	49·5	26·4	—	—	—	3·38	2·12	0·83
	T40°	90	47	20·4	32	16·8	—	—	—	3·38	2·17	0·84
13	H5°	90	72·6	43	51	16	96	57	68·6	3·66	2·80	0·83
	T40°	96	49	28·4	42·2	22	90	55	68·6	4·60	2·81	0·86
14	H	72	80·5	33	50·5	21·8	105	58	75	3·57	2·56	0·82
	T40°	84	48·2	23	27·6	—	101	58	77·5	4·21	2·93	0·94
15	H	90	56	28	33·6	26	130	76	95·6	3·42	2·11	0·80
	T40°	84	32	18	22	18	119	70	87	3·35	2·22	0·81
16	H	100	20	9	16	11	140	74	96	3·52	2·12	0·82
	T40°	100	16	5·5	10·5	3	130	65	83	3·37	2·13	0·85
17	H	70	24	12	17	13·5	94	51	68	3·23	2·30	0·76
	T40°	87	18	7·6	11·5	6·4	91·5	56	70	3·31	2·35	0·83
18*	H	120	176	71	100	43	107	64	76	9·70	1·21	0·73
	T40°	120	181	62	95	32	176	71	100	8·80	1·26	0·78
H	M	91	68	32	45	23	115	63	78	4·40	2·77	0·84
	S.D.	4·23			15·3	5·7			9·8	0·96		
	S.E.	1·02			3·7	1·4			2·5	0·23		
T 40°	M	94	48	22	32	16	108	64	78	4·50	2·82	0·85
	S.D.	13·9			11·5	6·2			8·6	0·95		
	S.E.	3·37			2·8	1·6			2·2	0·23		

* Case 18 was investigated after the statistical analysis was

TABLE I

ON TILTING FROM HORIZONTAL TO 40° FEET DOWN

Oxygen cons./m.²	P.A. sat'n.	B.A. sat'n.	A-V dif. vol %	Cardiac output	Cardiac index	Pulmonary resistances			Systemic resist.	Mitral area	Ventric. work kg./min./m.²		Case No.	Position
						Vasc.	Non-vasc.	Tot.			R	L		
112	63·2	94	6·25	2·75	1·79	—	—	2010	2118	—	1·81	1·70	1	H
123	64·3	96·8	6·55	2·90	1·88	—	—	1412	1811	—	1·41	1·60		T40°
156	62	92·5	7	4·30	2·23	353	353	706	1524	0·82	1·18	2·40	2	H
166	53·2	93	9·25	3·47	1·80	229	231	460	2065	0·94	0·50	2·13		T40°
166	35·6	92	8·56	2·88	1·93	1185	480	1665	2465	0·56	1·65	2·26	3	H
144	34·7	90·5	8·46	2·54	1·70	1132	466	1598	2800	0·52	1·24	2·01		T40°
213	51·7	89	5·65	5·94	3·76	349	307	656	1020	1·30	2·84	3·73	4	H
169	55	89·2	5·18	5·17	3·26	370	201	571	1265	1·47	2·01	3·51		T40°
171	49·8	91	8·47	3·73	2·01	150	515	665	1668	—	0·90	2·05	5	H
161	46·5	91·3	9·23	3·21	1·74	124	174	298	1987	—	0·31	1·81		T40°
172	54	91·5	6·28	3·66	2·73	437	326	763	—	—	1·37	—	6	H
176	52·6	95	7·10	3·32	2·47	385	313	698	—	—	1·04	—		T40°
176	58·2	91	5·12	5·62	3·43	354	370	724	935	1·09	2·32	2·93	7	H
188	58·9	93·2	5·35	5·75	3·50	277	305	583	1057	1·23	1·96	3·48		T40°
148	62	90·3	5·75	3·60	2·57	310	378	688	1881	0·74	1·17	2·87	8	H
152	60·6	91·5	6·25	3·40	2·43	163	330	493	2140	0·73	0·73	2·93		T40°
160	55	90·8	7·74	3·15	2·07	634	328	962	2131	—	1·13	2·28	9	H
158	50	92·6	9·2	2·60	1·71	552	154	706	2331	—	0·57	1·70		T40°
147	63·9	94·2	5·15	4·27	2·85	440	355	795	1215	0·82	1·93	2·40	10	H
171	60·8	96·2	6·0	4·50	3·00	267	195	462	1154	1·10	0·95	2·51		T40°
178	61	93	5·02	5·65	3·55	430	361	791	1060	0·99	2·91	3·47	11	H
180	58	94	5·65	5·08	3·18	189	251	440	1180	1·08	1·34	3·13		T40°
160	61·6	94	6·2	3·50	2·57	527	488	1015	—	—	1·64	—	12	H
155	62·8		5·95	3·51	2·58	345	269	614	—	—	1·02	—		T40°
131	50·8	85	7·02	2·49	1·86	800	665	1465	2200	0·48	1·25	1·65	13	H5°
163	50·8	87	7·4	2·94	2·19	549	462	1011	1860	0·65	1·20	1·95		T40°
140	62·3	91·4	4·87	4·54	2·87	506	298	804	1320	—	1·87	2·82	14	H
144	56·5	96	6·60	3·44	2·17	—	—	530	1800	—	0·71	2·21		T40°
162	57·7	93	5·27	5·45	3·07	111	309	420	1404	1·06	1·12	3·90	15	H
151	57	94·8	5·65	4·75	2·68	67	219	286	1466	1·13	0·53	3·07		T40°
166	74·2	94·3	3·8	6·47	4·36	62	74	136	1186	2·86	0·73	5·56	16	H
153	71	93·8	4·32	5·27	3·55	114		84	1259	—	0·32	3·88		T40°
140	69·3	95	4·6	5·06	3·04	55	134	189	1072	1·47	0·21	2·68	17	H
140	65·4	97·8	5·8	4·04	2·43	101	28	129	1384	2·81	0·25	2·21		T40°
224	33·4	76	9·0	3·44	2·5	1231	976	2207	1766	—			18	H
210	35·8	77·4	8·7	3·33	2·4	1428	632	2160	1844	—				T40°
158	58·3	91·7	6·45	4·29	2·74	413	390	894	1546		1·53	2·84	H	M
2·23	8·6	2·4	1·4		0·73	298			505		0·71	0·86		S.D.
0·54	2·0	0·6	0·3		0·17	77			130		0·17	0·22		S.E.
158	56·3	93·3	6·70	3·87	2·48	324	257	644	1705		0·94	2·54	T 40°	M
160	8·3	2·9	1·3		0·63	268			506		0·52	0·59		S.D.
0·38	2·0	0·7	0·3		0·15	69			130		0·13	0·15		S.E.

stical analysis was completed and is not, therefore, included in the mean figures.

ntilation ₂ cons. 100 ml.	R.Q.
3·31	0·81
3·11	0·80
2·80	0·84
2·75	0·86
3·30	0·83
3·47	0·86
3·01	0·83
3·22	0·90
2·43	0·85
2·38	0·78
3·75	1·05
3·87	1·10
3·04	0·86
3·01	0·84
3·03	0·85
2·83	0·79
3·21	0·88
3·23	0·85
2·48	0·85
2·65	0·84
2·82	0·79
2·95	0·79
2·12	0·83
2·17	0·84
2·80	0·83
2·81	0·86
2·56	0·82
2·93	0·94
2·11	0·80
2·22	0·81
2·12	0·82
2·13	0·85
2·30	0·76
2·35	0·83
1·21	0·73
1·26	0·78
2·77	0·84
2·82	0·85

may have led to error in calculating the diastolic filling pressure. In the five patients in whom it was measured, the intrathoracic pressure showed a wider respiratory excursion when recumbent but little or no change in mean pressure.

The rapidity with which tracings could be taken after changing position was limited by the time needed to reset the zero reference point—about one minute. On tilting, the pressures were found to have reached their lowest point already and remained stable thereafter for the duration of the tilt, which did not exceed twenty minutes. Similarly, the pulmonary pressures were found to have returned to pre-tilt levels on restoration to horizontal, in six of nine observations in which they were thus checked. In one case the pressures and pulmonary resistances exceeded pre-tilt figures and in the other pressures persisted 5 and 7 mm. Hg respectively below the initial figure. All these data are tabulated in Table I.

Discussion

Our data show that tilting from recumbency to 40° feet-down in cases of mitral disease has very little effect on several important aspects of circulatory dynamics. Thus the pulse rate and the systemic blood pressures were virtually unchanged; with the exception of the cases with trivial mitral disease cardiac output changes were small; and, although the systemic resistance tended to rise in most of them, the changes were relatively slight. The constancy of the oxygen consumption and the respiratory quotient suggests that the positional change did not alter metabolism. The major effects were confined to pulmonary dynamics and the absence of changes elsewhere renders the technique particularly valuable for the investigation of the pulmonary circulation.

The drop in intra-pulmonary pressures so frequently observed cannot be ascribed to a more negative intra-thoracic pressure, for the systolic and diastolic pulmonary arterial and the PCV pressures did not move in parallel. Moreover, the intrathoracic pressure recordings did not reveal a change in mean pressure. The fall was always greater than the conceivable zero-reference point error. We have been unable to find any previous reports on the effects of tilting on pulmonary dynamics in mitral disease and little has been published on the effects in normal subjects or in other disease states. In one normal subject and in one patient with essential hypertension tilted to 60°, Lagerlof *et al.* (1951) reported a fall in both pulmonary arterial and capillary pressures and cardiac output, and a rise in the calculated total and pulmonary vascular resistances; they also estimated the cardio-pulmonary blood volume by the Hamilton dye-dilution method and found it to diminish in both cases. There is general agreement that the lung blood volume is less in the erect position (Gilmore *et al.*, 1952; Sjostrand, 1953) and, in an ingenious series of experiments Sjostrand (1952) showed that this blood is transferred from the heart and lungs to the legs and in magnitude may be as much as 25 per cent of the cardio-pulmonary volume. This shift has been held responsible for the observed increase, on standing, in vital capacity and lung compliance (McMichael and McGibbon, 1939–42; Attinger *et al.*, 1956). Although we did not measure the lung blood volume, the evidence is so uniform that it is reasonable to assume a reduced blood volume on tilting. It is also reasonable to assume that the drop in lung blood volume is basically responsible for the fall in pulmonary pressures.

We have already observed that except in the cases with normal hæmodynamics, the pulmonary arterial and capillary venous pressure do not move in parallel. It seems unlikely, therefore, that the pressure changes are simply the result of altered lung blood volume and/or cardiac output. In a rigid system a diminution in volume will cause a general drop in pressure in the various parts of the vascular bed and the forward flow will be affected in accordance with the relations expressed in Poisuelles equation; this should not effect the calculated hindrances. In an elastic system reduction in distending pressure mediated through volume changes should cause an increase in hindrance, not the converse, for the lumen of the vessels will diminish, and Borst *et al.* (1956) have found this to be so in animal lungs. The only means whereby a satisfactory mechanical explanation can be afforded is by treating the site of pre-capillary hindrance, the "pulmonary vascular resistance", as an orifice through which flow is turbulent, as in the general hydraulic equation used by Gorlin and Gorlin

(1951). Under these circumstances, if the drop in pressure causes a fall in output, this fall is related to the square root of the pressure change; a fall in flow would then be accompanied by a fall in calculated resistance and this is made plain in the curves published by Gorlin and Gorlin (Fig. 6). This formula is hardly applicable to flow in a tube, and if it were there should be a direct relation between the change in resistance and the cardiac output on the one hand and the initial resistance on the other; this does not appear to be so. It might also be argued that a fall in pulmonary or venous pressure may affect vascular hindrance by reducing interstitial pressure and therefore the external pressure on the small non-muscular vessels. Morphologically the location of the resistance would appear to be the small muscular arteries prior to the capillary bed (Henry, 1952) and it seems unlikely that external pressure changes of a few millimetres of mercury would affect their lumen to any great extent. It is difficult to avoid concluding that, when a fall in pulmonary vascular resistance occurs, it is due to some degree of vasodilatation.

There is a strong suggestion in our data, and this is especially well seen in Fig. 4 that the response to tilting in those cases with moderate elevation of the pulmonary resistance (300 to 800 units) differs both from the normal response and from that seen in cases with a very high resistance. The two patients with mitral disease so slight as to be hæmodynamically normal both responded with a parallel fall in PA and PCV pressures, but with a considerable drop in cardiac output and therefore an increase in calculated resistance. This is the type of response found by Lagerlof *et al.* (1951) in two normal subjects. We also found, in two patients in whom tilting to 40° had reduced the PCV and pulmonary vascular resistance to normal limits, that further tilting to 60° caused a rise in resistance (unpublished data). The reason for the greater fall in output in normal subjects is apparent in the pressure/flow curves at the mitral valve (Fig. 6); the larger the valve the greater the change in flow for a given change in pressure. The relative constancy of the pulmonary arterial/venous pressure gradient at physiological pressures, despite the drop in volume and output, suggests a capillary bed operating close to a critical closing pressure.

There are only two cases in this series, with a very high vascular resistance (over 1000 units), but it is noteworthy that in one there was no appreciable change and in the other an increase in resistance on tilting. In the middle ranges with resistances of 300 to 800 units ten of the eleven cases showed a considerable drop in resistance and we have already concluded that this is probably due to vasodilatation. The method whereby this vasodilatation is brought about is not clear. It may be, as has been previously suggested, that vascular resistance is linked to the PCV pressure (Wood, 1954; Wade *et al.*, 1956) but this is clearly not so in Case 18 in which the initial resistance was 1231 units rising to 1428 on tilting despite a fall in PCV from 43 to 35 mm. There would seem to be some support here for the views of Harris (1957) that very high resistances will not yield to vasodilators, in his case acetylcholine, and are therefore presumptively due to organic obstruction rather than vasocontraction. This view must be accepted with some reserve, however, for after successful valvotomy, even extremely high pulmonary vascular resistances may fall rapidly (Mackinnon *et al.*, 1956). Moreover, there are many similarities between these cases and some of those with unexplained pulmonary hypertension, and it has been suggested that in some of these the increased hindrance is due to vasocontraction (Wade and Ball, 1957). If, as seems probable, there is a linkage, in the middle group, between the PCV pressure and the vascular resistance, the behaviour of the systemic resistance argues against sympathetic meditation. Brigden *et al.* (1950) demonstrated skin vasoconstriction on tilting while, in our cases, there was a general tendency for the systemic resistance to rise; it seems unlikely that a sympathetically mediated vasodilatation would occur in the lungs at a time when sympathetic tonus elsewhere is increased. These data support the view expressed by Wade *et al.* (1956) that the hypotensive effect of hexamethonium in some cases of mitral disease is not due to direct blocking of sympathetic nerve impulses to the lungs.

The fall in "non-vascular" resistance, which in some cases was the major factor in reducing the total pulmonary resistance, can largely be explained by the form of the pressure-flow curves at the mitral orifice (Fig. 6), for resistance will be related to flow changes as the tangent of this curve. The differences in calculated valve area in the two positions were generally small and only in one was

there an appreciable discrepancy (Case 17). This patient had mitral regurgitation as well as stenosis clinically, although the PCV curve did not show a large systolic wave, and possibly this has led to an error in calculating the orifice size. The difference in the other cases are all within the error of the method which has been assessed by Rodrigo (1953) as ± 50 per cent.

In addition to a fall in mean pressure, the PCV curve frequently changed in form, in that, when there were definitive waves they diminished in size; the converse was never observed. In six cases the major wave was late systolic and there is general agreement that this wave represents the *V* wave of the auricular pulse. Wade *et al.* (1952) showed that this wave was augmented in mitral regurgitation and suggested that it did not exceed 8 mm. Hg unless this was present. By these criteria the mitral valve was incompetent in recumbency but became competent on tilting in five patients. It seems unlikely that this reflects a true variation in valvular competency, but rather changes in the elasticity of the pulmonary-venous-left-atrial system at different pressure levels. There was no obvious correlation between the height of the recumbent pressure and the fall on tilting such as Oser *et al.* (1955) reported for the right atrium in cases of congestive heart failure.

Tilting has a striking differential effect on ventricular work. Right ventricular work diminishes by some 40 per cent, mainly on account of the fall in pulmonary arterial pressure, while left ventricular work drops by only 10 per cent entirely due to the slight fall in output.

The consistent and significant increase in the oxygen content of the systemic arterial blood can be explained in three possible ways. (1) There may be impairment of ventilation in recumbency and Blair and Hickam (1955) have shown that, in normal subjects, portions of lung are more slowly ventilated in this position; (2) there may be an alteration in the diffusing capacity of the lungs, and Carroll *et al.* (1953) have claimed that oxygen diffusion is impaired in the congested lung of mitral disease; or (3) there may be changes in the amount of venous admixture. Our data do not enable us to differentiate between these various possibilities. It seems improbable that these changes in systemic arterial oxygen content are related to the altered pulmonary vascular resistance for, although breathing pure oxygen will often lower the raised pulmonary resistance in mitral disease (McGregor *et al.*, 1953), the changes in our cases were small and did not correlate well, in individual cases, with the change in resistance. Pulmonary arterial blood oxygen also seemed unimportant, for the relation between this and the resistance was generally inverse.

Conclusions

Hæmodynamic findings are reported in eighteen patients suffering from mitral disease who were studied recumbent and also when tilted feet-down at an angle of 40° from the horizontal.

On tilting, the pulmonary arterial and capillary pressures and the total pulmonary vascular resistance invariably fell. The pulmonary vascular resistance rose in two patients with normal hæmodynamic findings, fell in all but one of those with a moderately raised resistance, and rose in one and was unchanged in the other of two cases with a very high resistance. It is concluded that a fall in pulmonary vascular resistance probably represents vasodilatation, that this is brought about indirectly by a diminution in lung blood volume, and that the autonomic nervous system is probably not involved.

The form of the pulmonary capillary venous curve was frequently altered, definitive waves, if present, becoming smaller.

The pulse rate, systemic blood pressure, oxygen consumption, and respiratory quotient did not alter with the change in position. Cardiac output changes were usually small.

It is suggested that tilting is a useful method for investigating pulmonary dynamics with minimal interference with other aspects of the circulation.

We thank Dr. Morgan Jones for his help and for permission to study patients under his care, Mr. R. C. de Meneaud for his technical assistance and Miss K. M. Lamb for secretarial help. We also thank our patients for their tolerant co-operation.

References

Attinger, E. O., Monroe, R. G., and Segal, M. S. (1956). *J. Clin. Invest.*, **35**, 904.
Blair, E., and Hickam, J. B. (1955). *J. Clin. Invest.*, **34**, 383.
Borst, H. G., McGregor, M., and Whittenberger, J. L., Berglund, E. (1956). *Circ. Res.*, **4**, 393.
Brigden, W., Howarth, S., and Sharpey-Schafer, E. P. (1950). *Clin. Sci.*, **9**, 79.
Carroll, D., Cohn, J. E., and Riley, R. L. (1953). *J. Clin Invest.*, **32**, 510.
Davies, L. G., Goodwin, J. F., and Van Leuven, B. D. (1954). *Brit Heart J.*, **16**, 440.
Dornhorst, A. C., and Leathart, G. L. (1952). *Lancet*, **2**, 109.
Fowler, N. O., Westcott, R. N., Hauenstein, V. D., Scott, R. C., and McGuire, J. (1950). *J. Clin. Invest.*, **29**, 1387.
Gilmore, H. R., Kopelman, H., McMichael, J., and Milne, I. G. (1952). *Lancet*, **2**, 898.
Gorlin, R., and Gorlin, S. G. (1951). *Amer. Heart J.*, **41**, 1.
Harris, P. (1957). *Brit Heart J.*, **19**, 272.
Henry, E. W. (1952). *Brit. Heart J.*, **14**, 406.
Lagerlof, H., Eliasch, H., Werko, L., and Berglund, E. (1951). *Scand. J. Clin, Lab. Invest.*, **3**, 85.
Mackinnon, J., Vickers, C. F. H., and Wade, E. G. (1956). *Brit Heart J.*, **18**, 442.
McGregor, M., Bothwell, T. H., Zion, M. M., and Bradlow, B. A. (1953). *Amer. Heart J.*, **46**, 187.
McMichael, J., and McGibbon, J. P. (1939). *Clin. Sci.*, **4**, 175.
——, Sharpey-Schafer, E. P. (1944). *Brit. Heart J.*, **6**, 33.
Meriel, P., Botinelli, R., Calazel, P., and Cassagneau, J. (1953). *Arch. Mal. Cœur*, **46**, 329.
Oser, B., Huston, J. R., and Ryan, J. M. (1955). *Clin Res. Proc.*, **3**, 197.
Rodrigo, F. A. (1953). *Amer. Heart J.*, **45**, 1.
Scott, R. C., Kaplan, S., and Stiles, W. J. (1955). *Amer. Heart J.*, **50**, 720.
Sjostrand, T. (1952). *Acta. Physiol. Scand.*, **26**, 312.
—— (1953). *Physiol. Rev.*, **33**, 202.
Stead, E. A., Warren, J. V., Merrill, A. J., and Brannon, E. J. (1945). *J. Clin. Invest.*, **24**, 326.
Storstein, O., and Tveten, H. (1954). *Scand. J. Clin. Lab. Invest.*, **6**, 169.
Wade, E. G., Werko, L., Eliasch, H., Gidlund, A., and Lagerlof, H. (1952). *Quart. J. Med.*, **21**, 361.
—— Mackinnon, J., and Vickers, C. F. H. (1956) *Brit. Heart J.*, **18**, 458.
—— Ball, J. (1957). *Quart. J. Med.*, **26**, 83.
Wood, P. (1954). *Brit. med. J.*, **1**, 1051.

SERUM GLUTAMIC OXALACETIC TRANSAMINASE LEVELS IN DIPHTHERITIC MYOCARDITIS

BY

E. CHESLER

From the Johannesburg Fever Hospital, Johannesburg

Received July 29, 1957

Serum glutamic oxalacetic transaminase (S.G.O.T.) is normally present in human serum, skeletal muscle, brain, liver, kidney, testis, and lung. Its highest concentration, however, is in cardiac muscle. Elevated S.G.O.T. levels occur with active dissolution of the tissues containing this enzyme and abnormally high levels are associated with cardiac cellular necrosis. This elevation is directly related to the extent of tissue destruction (LaDue *et al.*, 1954; LaDue and Wroblewski, 1955; Nydick *et al.*, 1955).

In the cases presented here, serial S.G.O.T. levels estimated during the course of severe diphtheria are compared with concomitant electrocardiograms.

Case Reports

Case 1. An 8-year-old boy was admitted with the complaint of sore throat for six days and difficulty in breathing for one day. Examination showed an extremely ill boy with laryngeal stridor, sternal recession, and obvious "bull-neck" lymphadenopathy. The tonsils, uvula, and pharynx were covered with diphtheritic membrane. The remainder of the physical examination was negative. 120,000 units of anti-diphtheritic serum was given intramuscularly and a tracheotomy performed; intramuscular penicillin and oral prednisone

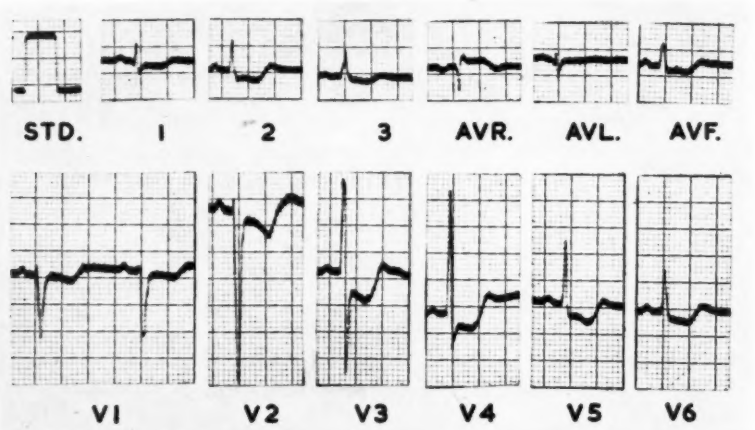


FIG. 1.—Cardiogram of Case 1, showing abnormal changes during the course of myocarditis.

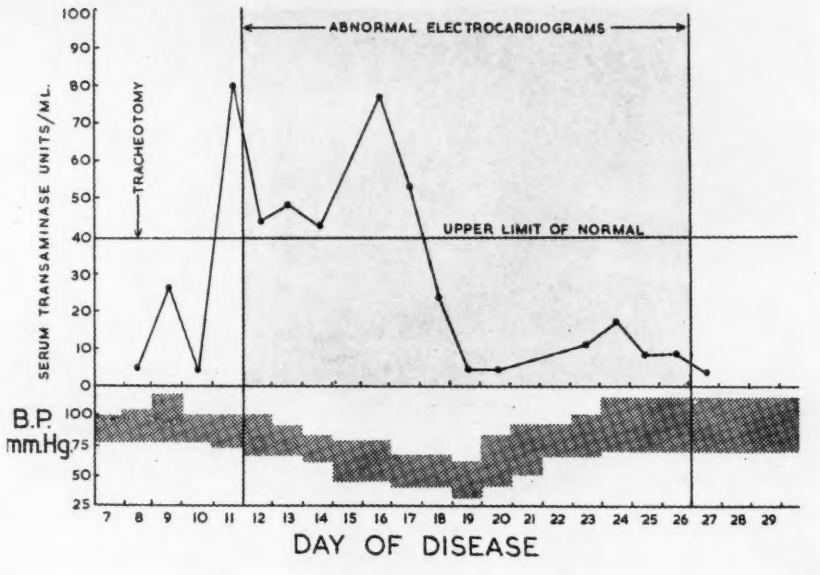


FIG. 2.—Diagram showing relationship of S.G.O.T. levels to cardiac changes in Case 1.

and oxytetracycline were given post-operatively. On the twelfth day of the disease he showed clinical evidence of carditis manifested by vomiting, marked increase in pallor, hypotension, and cardiac enlargement. Electrocardiographic abnormalities were also noted at this time (Fig. 1) and persisted for fourteen days. At no stage were there signs of congestive cardiac failure.

Laboratory Investigations. A virulent strain of *C. diphtheriæ* was isolated from the throat swabs. Serial S.G.O.T. estimations are shown in Fig. 2. Electrocardiograms recorded on the seventh and ninth day of disease were normal. The cardiograms on the eleventh day when the S.G.O.T. level was 80 units per ml., showed doubtful depression of the S–T segments. Cardiograms from the twelfth day onwards revealed progressive depression of the S–T segments in epicardial leads, with reciprocal S–T elevation in cavity leads, and flattening or inversion of the T waves. Maximum depression of the S–T segment of 5 mm. was noted on the sixteenth day following which there was a slow return to normal, and iso-electric S–T segments with upright T waves were once again recorded on the 27th day of the disease. On the sixteenth and the eighteenth days there was complete A-V dissociation. A representative cardiogram is shown in Fig. 1.

Case 2. A 7-year-old boy was admitted on the seventh day of his illness. Examination disclosed extreme toxæmia associated with a "bull-neck" lymphadenopathy, and membrane formation on the tonsils, uvula, and pharynx. The remainder of the physical examination was negative. He was given 50,000 units of anti-diphtheritic serum and penicillin and oxytetracycline orally. There was little improvement in his condition and on the ninth day of the disease he complained of persistent nausea, epigastric and substernal pain, and vomited repeatedly. His blood pressure dropped from 110/70 to 80/60 mm. Hg and cardiac enlargement was noted. From the tenth to the sixteenth day of the disease a reversed split of the pulmonary second sound was heard. By the eighteenth day of the disease he was asymptomatic and his heart size had returned to normal. At no stage was there evidence of congestive cardiac failure.

Laboratory Investigations. A throat swab yielded a virulent strain of diphtheria bacillus. Serial S.G.O.T. estimations are shown in Fig. 3.

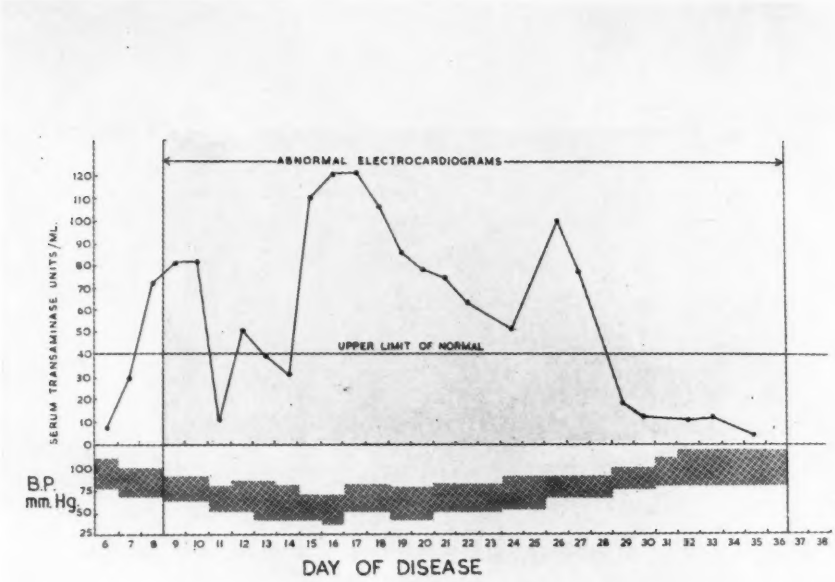


FIG. 3.—Diagram showing relationship of S.G.O.T. levels to cardiographic changes in Case 2.

Electrocardiograms. Day 5, 6 and 7: Normal.

Day 8: Sinus rhythm. Probable early depression of the S–T segments and flattening of the T waves.

Day 9: Sinus rhythm; definite depression of the S–T segments in epicardial leads with S–T elevation in cavity leads. T waves flattened or inverted.

Day 10: Complete A-V dissociation and left bundle branch-block.

Day 11: Sinus rhythm. Grade 1 A-V block (P–R interval 0·24 sec.) and left bundle-branch block.

Day 12, 13 and 14 (Fig. 4a): Sinus rhythm with Grade 2 heart block, Wenckebach periods, and left bundle-branch block.

Day 15 (Fig. 4b) and 16: Complete A-V dissociation and left bundle-branch block. The elevated S–T segments usually recorded by right ventricular epicardial leads in left bundle-branch block were now markedly depressed in leads VI to V3: further depression of the S–T segments in leads V4 to V6 is also evident.

Day 17: Sinus rhythm. Grade 1 A-V block (P–R interval 0·3 sec.). The abnormalities of the S–T segments and the T waves were still evident, but the pattern of left bundle-branch block had disappeared.

From the 18th day onwards, a progressive return of the S–T segment to the iso-electric line and reversion of the T waves to normal occurred. On the 37th day of disease a completely normal cardiogram was recorded.

Case No. 3: A 7-year-old boy was admitted on the fourth day of his illness. He was critically ill, with laboured respiration as a result of membrane formation in the throat and nose with accompanying soft tissue œdema. Massive "bull-neck" lymphadenopathy was present. The blood pressure was 68/40 mm. Hg. The extremities were cold and cyanosed. There was no clinical evidence of carditis. 120,000 units of anti-diphtheritic serum were given intramuscularly and a tracheotomy performed. In addition, he received penicillin, oxytetracycline, hydrocortisone, and nor-adrenaline. There was no response and he died in peripheral circulatory failure after 36 hours in hospital, on the 6th day of the disease. Throat swabs yielded a virulent

strain of diphtheria bacillus. On the fifth day of the disease the electrocardiogram was normal, and the S.G.O.T. was 20 units per ml.

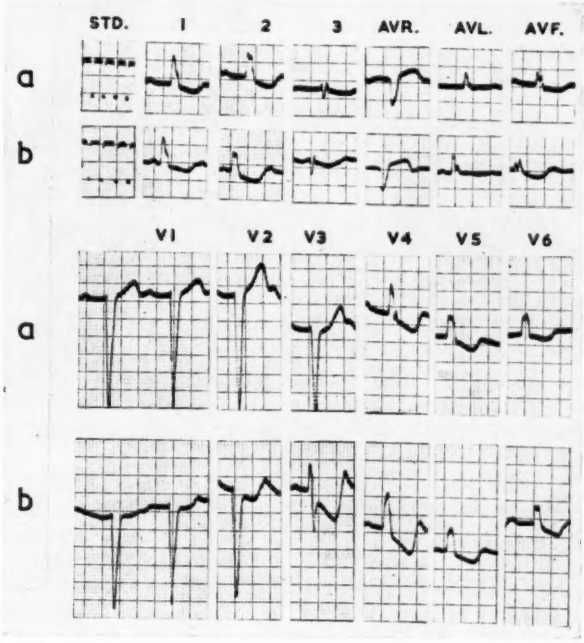


FIG. 4.—Cardiogram of Case 2, showing abnormal changes observed during the course of myocarditis on the fourteenth and the fifteenth days (a and b, respectively).

Case 4. A girl of 10 years was admitted on the twelfth day of her illness. Examination revealed a severe "bull-neck" diphtheria. She was given penicillin, oxytetracycline and prednisone. Throughout her stay in hospital, there was no evidence of myocarditis. Throat swabs yielded a virulent strain of C. diphtheriæ. The S.G.O.T. levels are shown below.

Day of disease	11	12	13	14	15	16	17	18	19	20	21	22	24	25	26	27	28	40
S.G.O.T. (units per ml.) ..	5	5	5	5	9	14	28	27	21	7	5	23	61	24	41	24	5	6

Case 5. A girl, aged 3 years, was admitted on the fifth day of her illness. There was extensive membrane formation in the throat and larynx necessitating a tracheotomy shortly after admission. "Bull-neck" lymphadenopathy was present. She was treated with 40,000 units of anti-diphtheritic serum, penicillin, and oxytetracycline. At no stage in the disease was there clinical or cardiographic evidence of myocarditis. Throat swabs yielded a virulent strain of C. diphtheriæ. The S.G.O.T. levels are shown below.

Day of disease	6	8	9	10	11	13	14	15	16	17	18	20	21	22	23	24	25
S.G.O.T. (units per ml.) ..	31	24	11	5	31	15	5	31	25	9	46	42	59	59	46	16	6

Case 6. A boy, aged 2 years, suffering from "bull-neck" diphtheria was admitted on the sixth day of his illness. He was treated with penicillin, anti-diphtheritic serum, and oxytetracycline, but on the tenth day of disease he developed clinical evidence of myocarditis. Electrocardiogram showed left bundle-branch block, gross depression of the S–T segments in epicardial leads, with S–T elevation in cavity leads. Despite supportive therapy, he died three days later. S.G.O.T. estimations on the tenth and twelfth days were 88 and 220 units per ml. respectively.

Discussion

In diphtheria, clinical and cardiographic evidence of myocarditis is commonly observed during the second week of the disease (Wood, 1956). In the six cases presented here, serial S.G.O.T. estimations and daily cardiograms were performed during, and preceding this period. In Cases 1, 2, and 6, the clinical diagnosis of carditis was substantiated by cardiographic studies. In Cases 1 and 2, an elevated S.G.O.T. level was noted a day before the first unequivocally abnormal cardiogram and persisted during the period of worst carditis, returning to normal levels (below 40 units per ml.) several days before regression of cardiographic changes. In Case 2, after the onset of carditis, the sharp rise in the S.G.O.T. level on the 15th day (Fig. 3) coincided with cardiographic evidence of further cardiac damage at this time (Fig. 4). In Cases 3, 4, and 5, there was no clinical or cardiographic evidence of carditis, despite the early manifestations of severe toxæmia. In Case 3, where death occurred due to peripheral vascular failure, a normal S.G.O.T. of 20 units per ml. was obtained and the marked systemic effects of the diphtheria toxin in the absence of myocarditis, did not result in an elevated S.G.O.T. level. In Cases 4 and 5, there was a transient rise in the S.G.O.T. at about the 24th and 18th days respectively.

A constant feature of diphtheritic myocarditis is hyaline degeneration and necrosis of muscle fibres (Gore, 1948). The release of glutamic oxalacetic transaminase into the circulation from injured cardiac muscle provides an index of active cellular damage. Consequently, the early elevated levels may be expected to return to normal sooner than the cardiographic changes which continue to reflect abnormal patterns as a result of ensuing fibroblastic repair. The transient slight elevation of the S.G.O.T. levels in Cases 4 and 5 may be due to minimal myocardial damage insufficient to produce clinical and cardiographic abnormalities, and could be a pointer to the exercise of caution in the early ambulation of such cases.

Further study of the S.G.O.T. levels in diphtheritic myocarditis may demonstrate this test to be of considerable value in the early diagnosis of this condition. It may prove to be particularly useful in those cases where carditis is suspected clinically but cardiographic studies are inconclusive.

Summary

Serial S.G.O.T. estimations with daily electrocardiograms were carried out in six cases of severe diphtheria. Three cases complicated by myocarditis showed abnormally elevated levels which correlated well with the cardiographic studies.

I am greatly obliged to Dr. A. L. Jackson, Superintendent of the Johannesburg Fever Hospital for permission to publish these cases. My thanks to the South African Institute for Medical Research for the laboratory investigations. I am indebted to Dr. R. M. Brueckner for permission to study one of her cases and to Dr. L. Schamroth for constant advice and helpful criticism.

References

LaDue and Wroblewski, F. (1955). *Circulation*, **11**, 871.
——, ——, and Karmen, A. (1954). *Science*, **120**, 497.
Nydick, I., Wroblewski, F., and LaDue, J. S. (1955). *Circulation*, **12**, 161.
Wood, P. (1956). *Diseases of the Heart and Circulation.* 2nd ed., Eyre and Spottiswoode, London.
Gore, I. (1948). *Amer. J. med. Sci.*, **215**, 257.

THORACOLUMBAR SYMPATHECTOMY IN HYPERTENSION

By W. E. PARKES

From the Royal Victoria Hospital, Belfast

Received July 30, 1957

The average survival time of patients in the malignant phase of hypertension is short—eight months according to Keith *et al.* (1928). There have been many reports of the effects of bilateral thoracolumbar sympathectomy on the mortality rate in this disease. Woods and Peet (1941) recorded a survival rate of 33 per cent five years after operation and Peet and Isberg (1946) a rate of 19 per cent after five to eleven years. Evelyn *et al.* (1949) noted that in twelve of their patients papillœdema disappeared but there was no significant fall in blood pressure. In England, Morrissey *et al.* (1953) have had encouraging results in the treatment of severe hypertension, but Pickering (1955) recorded an adequate fall in blood pressure in only 18 per cent of 142 patients two years after operation.

Bilateral thoracolumbar sympathectomy is a major surgical procedure and may be followed by troublesome complications such as causalgia and postural hypotension. Many centres have, therefore, abandoned the operation in favour of "medical sympathectomy" by ganglion-blocking drugs. Unfortunately, not all the patients suffering from severe diastolic hypertension respond adequately to these drugs. The recently introduced mecamylamine is said to be more effective than the other ganglion-blocking agents, but it has a potent vagal blocking effect. In view of the difficulty in connection with ganglion-blocking drugs, it was thought that a review of the results of thoracolumbar sympathectomy in this hospital would be of value.

Before operation all patients had undergone a full clinical examination, followed by examination of the urine, specific gravity range test, blood urea estimation, intravenous pyelogram, and by cardioscopy, electrocardiogram, and a sedation test. A few had slight albuminuria, but none had significant impairment of renal function or evidence of cardiac failure. Only one was over the age of 50. The positive indications were a persistent diastolic blood pressure above 130 mm. Hg or intractable headaches and rapid deterioration of vision. The headaches were intense in 27 of the 31 patients.

RESULTS

This report deals with 31 patients who attended for review 6 months to 8 years after thoracolumbar sympathectomy of the Smithwick type with splanchnicectomy and removal of the sympathetic chain from at least T8 to L2 or 3: in several instances the sympathetic chain was removed up to T4. Six patients had malignant hypertension.

The data are sumarized in Table I. The initial blood pressure refers to the lowest reading before therapy was started, and in most patients this was obtained after a few days in hospital. The basal pressure was the lowest obtained during the sodium amytal sedation test. A significant fall in blood pressure was regarded as one over 30 mm. systolic and over 20 mm. Hg diastolic. This occurred in approximately 32 per cent of the series over a period of 6 months to 8 years.

The average blood urea before operation was 31·2 mg. per 100 ml. The last assessment after operation showed a rise in the blood urea in 5 patients, the highest figure being 51 mg. per 100 ml.

The electrocardiographic changes were much improved in 8 patients, and an example is shown in Fig. 1. The left ventricular enlargement was appreciably reduced in 10 patients.

TABLE I

RESULTS OF THORACOLUMBAR SYMPATHECTOMY OPERATIONS

No.	Lowest blood pressure before therapy	Sex	Age	Lowest blood pressure with sodium amytal	Post-operative assessment			
					No. of months after operation	Blood pressure		
						Recumbent	Standing	On oral reserpine & hydrallazine
1	260+/180	F	44	210/140	37	260/155	230/150	170/120
2	240/125	F	45	230/110	22	230/130	160/115	175/100
3	190/130	M	40	180/130	28	180/110	160/115	—
4	230/125	F	46	230/125	7	180/105	—	—
5*	205/135	F	38	170/115	58	170/110	140/105	—
6*	200/100	F	39	190/105	20	220/110	190/110	—
7	230/150	M	38	210/125	36	125/95	130/100	—
8*	235/130	F	45	230/130	44	165/100	155/105	—
9	220/130	F	44	220/125	70	220/135	220/135	170/100
10	220/140	F	33	220/140	47	155/100	140/105	—
11	260+/160	F	42	240/150	52	190/135	190/140	190/105
12	250/135	M	55	200/125	33	220/170	175/140	—
13	260/140	M	43	195/125	62	190/110	169/110	—
14	180/120	F	42	180/120	56	160/95	150/100	—
15	240/135	F	31	190/125	45	170/100	200/110	—
16	210/120	F	46	205/110	21	160/100	150/100	—
17	265/160	F	55	195/105	13	200/95	200/100	—
18	—	F	39	230/130	47	180/105	180/125	—
19	195/110	F	45	190/110	102	230/130	170/115	—
20	240/175	M	34	210/140	26	215/130	180/130	120/90
21	260/180	M	48	220/140	47	220/135	165/120	—
22	220/150	F	43	180/140	17	170/110	—	—
23	210/150	M	21	220/140	6	220/150	190/145	—
24	—	M	42	245/135	59	140/100	95/65	—
25	180/150	M	29	170/125	11	150/100	135/100	—
26	230/130	M	50	215/115	6	210/140	195/140	180/110
27	240/165	F	20	220/140	16	155/130	165/140	160/90
28	240/160	F	30	200/140	14	250/160	220/155	—
29	260/140	F	46	220/110	15	260/130	250/130	190/105
30	—	F	48	235/140	72	165/100	175/115	—
31	250/150	M	25	250/145	19	170/110	150/110	—

* Patients who had first stage sympathectomy only.

After operation symptoms included exertional dyspnœa in 9 patients, residual headaches in 4, vertigo in 1, angina pectoris in 2, and a variable degree of postural hypotension is several cases. All patients who had previously complained of intense headaches felt that the operations had been well worth while.

DISCUSSION

The effectiveness of thoracolumbar sympathectomy has been widely debated. Platt and Stanbury (1950) say "sympathectomy may be justifiable as a symptomatic measure for the relief of crippling headaches; but in a few patients relief may be bought at the price of new symptoms ... Some have exchanged severe headaches for severe exertional tachycardia and fatiguability". This is an extreme view, although the criticism is quite justifiable and was noted in the above series. The attitude of Rosenheim (1954) and Wells (1956) is more acceptable. They feel that the pendulum has swung too far away from operation and that there will probably be a continued and perhaps increasing demand for it in carefully selected cases.

As Fishberg (1954) points out, there is no evidence that sympathectomy is other than the production of one physiological derangement to counteract another. The dilatation of the splanchnic vessels

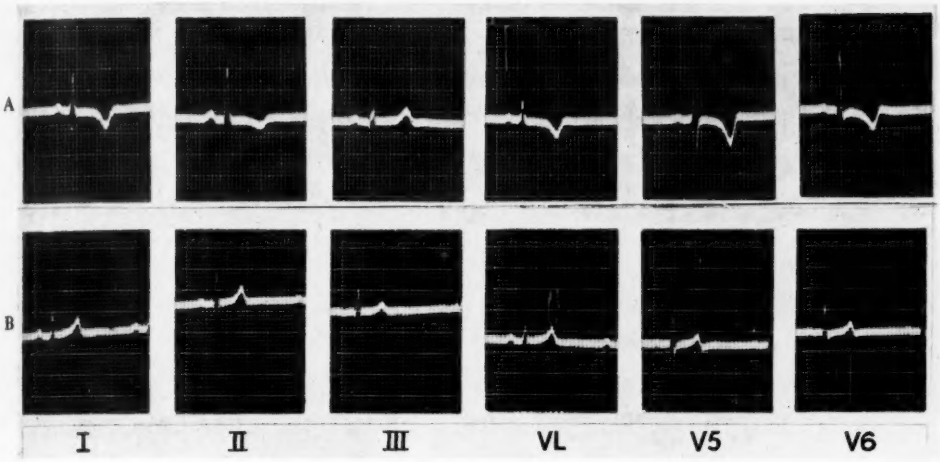


FIG. 1.—Electrocardiogram (A) before treatment (4/4/55), and (B) eight months afterwards (7/12/55), showing improvement in the T waves.

plays an important part in the hypotensive effect of sympathectomy. This may last for months or years but the diminution of peripheral resistance produced by sympathectomy may diminish as time goes by. Nevertheless the average survival time of patients who have had sympathectomy operations is much greater than could be expected without operation. Smithwick (1951) found that the mortality in 77 cases of malignant hypertension was 56 per cent, 5 to 12 years after operation, whereas in 174 medically treated nearly all had died.

There are several common post-operative complications. Following the second stage operation there is often profound hypotension: in one of the present series a nor-adrenaline intravenous drip had to be maintained for over 24 hours. Later, postural hypotension may be troublesome, but may be controlled by a firm abdominal binder. Pain due to cutting of the intercostal nerves at operation may require intercostal block.

There are two other complications that were not encountered in the present series. First, Blegan and Kintner (1947) report massive hæmorrhage from a peptic ulcer following a sympathectomy operation: one might expect this, as sympathectomy is the converse of vagotomy. Secondly, impotence has occurred in some young men, though in women sexual function does not seem to be disturbed.

The indications for thoracolumbar sympathectomy have varied over the years. At present it is agreed that hypotensive drugs should always be tried first. If these fail, the main indication is intractable headache with a persistently raised diastolic blood pressure. Secondly, if there is gross hypertensive retinopathy, in spite of medical treatment, the operation is indicated, as the vision can be much improved even if there is no subsequent fall in blood pressure.

Formerly the sodium amytal sedation test was widely used. If the blood pressure fell satisfactorily it was assumed that the patient would respond well to sympathectomy. In practice, no such correlation was found and the test has been abandoned.

Many contraindications to the operation have been suggested. It is seldom advised if the patient is over 50 years of age. It should never be advocated in the presence of significant impairment of renal function. Chavez and Mendez (1949) have described improvement in patients who were in cardiac failure before operation. Certainly gallop rhythm that persists despite bed rest, and the need for sodium restriction, digitalization, and mercurial diuretics may disappear after sympathectomy (Fishberg, 1954).

The final column in Table I, shows that in many of the patients who did not have a satisfactory fall in blood pressure after operation, this was obtained by oral reserpine and hydrallazine. Schroeder (1952) also found out that patients were more sensitive to hydrallazine following unsuccessful thoracolumbar sympathectomy and Grimson *et al.* (1952) note that patients previously treated by sympathectomy usually derive a good fall of blood pressure from small doses of hypotensive drugs. Reserpine and hydrallazine act centrally and, when used with care, cause less troublesome side-effects than the more potent autonomic ganglion blocking drugs.

The majority of sympathectomy operations described in this report were undertaken before the introduction of the recent hypotensive drugs. It will be of interest to determine whether patients who fail to respond to reserpine and hydrallazine before sympathectomy do so after the operation.

Summary

The results of thoracolumbar sympathectomy performed for severe hypertension have been reviewed.

Of 31 patients assessed at intervals varying from 6 months to 8 years after the operation 32 per cent showed a satisfactory fall in diastolic blood pressure. Many of those who failed to show a significant fall in blood pressure after this operation responded to combined oral reserpine and hydrallazine therapy.

Most of the patients were under the care of Dr. J. F. Pantridge who suggests this investigation. My thanks are also due to the late Mr. C. A. Calvert, who performed most of the operations and to Mr. A. R. Taylor and Mr. J. A. W. Bingham, who operated on the other patients.

References

Blegan, H. M., and Kinter, A. R. (1947). *J. Amer. med. Ass.*, **133**, 1207.
Chavez, I., and Mendez, L. (1949). *Amer Heart J.*, **37**, 523.
Evelyn, K. A., Alexander, F., and Cooper, S. R. (1949). *J. Amer. med. Ass.*, **149**, 592.
Fishberg, A. M. (1954). *Hypertension and Nephritis.* Baillière, Tindall and Cox, London.
Grimson, K. S., Orgain, E. S., Rowe, C. R., and Sieber, H. A. (1952). *J. Amer. med. Ass.*, **149**, 215.
Keith, N. M., Wagener, H. P., and Kernohan, J. W. (1928). *Arch. intern. Med.*, **41**, 141.
Morrissey, D. M., Brookes, V. S., and Cooke, W. T. (1953). *Lancet*, **1**, 403.
Peet, M. M., and Isberg, E. M. (1946). *J. Amer. med. Ass.*, **130**, 467.
Pickering, G. W. (1955). *High Blood Pressure.* J. and A. Churchill, London.
Platt, R., and Stanbury, S. W. (1950). *Lancet*, **1**, 651.
Rosenheim, M. X. (1954). *Brit. med. J.*, **2**, 1181.
Schroeder, H. A. (1952). *J. Lab. clin. Med.*, **38**, 949.
Smithwick, R. H. (1951). *J. Amer. med. Ass.*, **147**, 1611.
Wells, C. (1956) *Scot. med. J.*, **14**, 245.
Woods, W. W., and Peet, M. M. (1941). *J. Amer. med. Ass.*, **117**, 1508.

UNILATERAL RIB-NOTCHING FROM THE COLLATERAL CIRCULATION AFTER DIVISION OF THE SUBCLAVIAN ARTERY

BY

MAURICE CAMPBELL

From the Cardiac Department, Guy's Hospital, and the Institute of Cardiology

Received October 21, 1957

The operation of subclavian-pulmonary anastomosis has provided another cause for unilateral rib-notching—the collateral circulation to the arm after division of its subclavian artery. The flow is, of course, in the reverse direction to the flow in the collateral arteries that by-pass a coarctation of the aorta.

We are reporting three cases in which there was striking unilateral rib-notching after a subclavian-pulmonary anastomosis, in one with other signs of a collateral circulation in the chest wall. My attention was drawn to the first of these patients by Dr. Curtis Bain as long ago as 1949 (Fig. 1A), but I did not then see the explanation. I thought there might be some new collateral circulation to the lungs, for small arteries from the mediastinum had often been seen entering the hila in patients with Fallot's tetralogy. Barrett and Daley (1949) also drew attention to the arteries they had seen at this site coming from the mediastinal, phrenic, and internal mammary arteries.

It was not until several years later when this boy was re-examined and two further patients were seen, all of whom had rib-notching on the side where the subclavian artery had been divided, that the correct explanation became apparent. The point at which the subclavian is divided is not far from the usual site of a coarctation, and anastomotic vessels that can carry blood from some branches of the subclavian and axillary arteries to parts below the coarctation can do so equally well in the opposite direction, from the lower part of the chest wall to the axillary artery and the arm.

When discussing this conclusion with my radiological colleagues, Dr. Hills and Dr. Dow, I found that unilateral rib-notching after division of a subclavian artery had been described by Kent (1953). He was, I think, the first to link these two features and to suggest the right explanation. He reported two cases, both with rib-notching on the side of the operation. The first had a complex lesion, probably dextrocardia and tricuspid atresia, and the second did not have an anastomosis completed: but, as he says, this does not affect the argument, because the subclavian artery was divided in both—for a successful anastomosis in the first and for an attempted anastomosis in the second. Since his paper this syndrome has been observed by several radiologists: it does not, however, seem to be so widely known among physicians.

As will be seen later, the condition is much more common than has been supposed, though generally in a less striking form than in these three cases. Sometimes there are also signs of the collateral circulation in the chest wall. Thus in Case 1, there was a prominent pulsating artery passing over the right clavicle very similar to the one shown by Kent (1953, his Fig. 10) as well as arteries in the chest wall over the lower ribs.

Case Notes

To save repetition, some features common to all three patients will be given first. All three had subclavian-pulmonary anastomosis done by Sir Russell Brock in 1948 and all have developed

striking unilateral rib-notching on the side on which the subclavian artery was divided. Two had Fallot's tetralogy and were severely disabled (Cases 1 and 3) and the third who had tricuspid atresia was moderately disabled (Case 2). All three had been deeply cyanotic from infancy and all were polycythæmic, with the hæmoglobin raised to between 140 and 150 per cent and with clubbed fingers and toes. None had any signs of coarctation of the aorta and the highest systemic blood pressure was 105/75 mm. All three squatted before, but not after operation.

All were greatly improved after the operation and have kept well for nine years, so that they can now lead normal quiet lives and earn their living, one as an architect, one as a warehouseman, and one as a laboratory assistant. All have a continuous murmur over the site of the anastomosis.

In none of them was there any visible rib-notching in the films taken before operation. It is, I think, no more than coincidence that they all obtained very good results from the operation and that two of them had very small hearts before it (Cases 1 and 2) for these are not uncommon with morbus cœruleus.

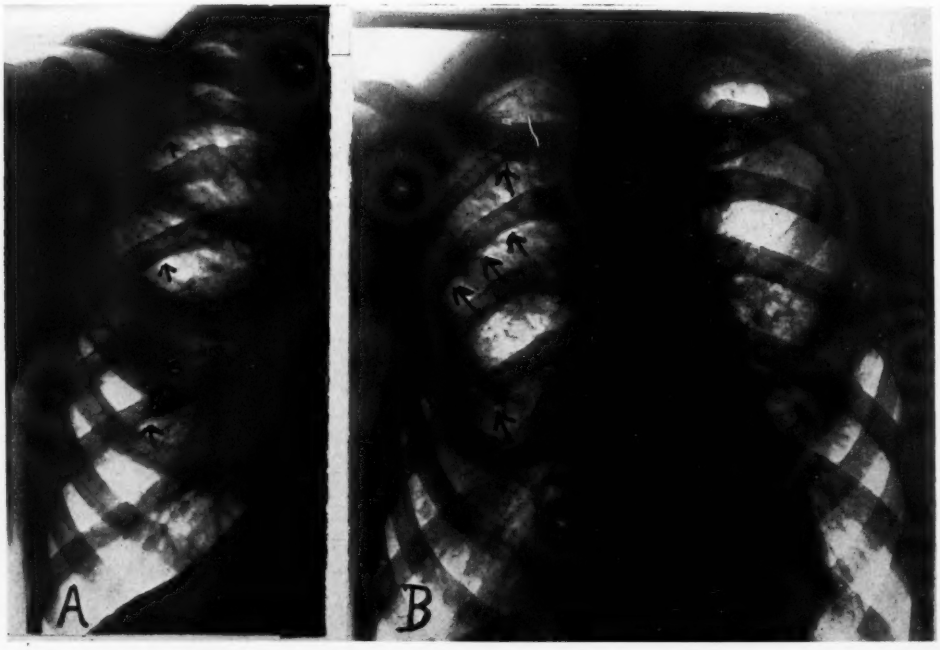


FIG. 1.—Case 1. Unilateral rib-notching on the right after a right-sided subclavian-pulmonary anastomosis for Fallot's tetralogy in 1948. (A) In 1950, (B) in 1957. Both show decisive rib-notching on the 4th, 5th, 6th, and 8th right ribs. The heart is not enlarged (c.t.r. 48 per cent).

Case 1. A boy, aged 13, had Fallot's tetralogy and could rarely walk more than twenty yards. He had a right-sided anastomosis in June, 1948. His improvement came slowly and at first we were afraid there might have been some thrombosis in the anastomosis but within three months the result was excellent and he was walking a mile and cycling.

In October, 1949, Dr. Curtis Bain, who had been seeing the patient for years, found a striking collateral circulation that had not been visible before and seemed to involve the internal mammary, vertebral, and intercostal arteries on the right side, with some rib-notching on this side. When seen by us in 1950 he was leading a normal life at school, except for games. He was much less cyanosed and polycythæmic and his hæmoglobin percentage was nearly normal. Large pulsating collateral arteries could be seen and felt over the clavicle and sternum, but we were less certain about the rib-notching on the X-ray film (Fig. 1A). The

femoral pulse was easily felt, the blood pressure normal, and there was no evidence of coarctation or of a past thrombotic obstruction of his aorta. I did not, at that time, think of the correct explanation.

Nine years after the operation he is extremely well, working regularly in a laboratory and leading a normal quiet life. The cyanosis is slight and the hæmoglobin has fallen from 148 before operation to 114 per cent. The heart is larger but still within normal limits for it had been very small before (c.t.r. 41% in 1948, 48% in 1950 and in 1957). The superficial collateral circulation is less obvious as he has put on weight, but can easily be seen and felt over the lower rib spaces and where a prominent artery passes across the right clavicle. The rib-notching is now more obvious (Fig. 1B) mainly on the 4th, 5th, 6th, and 8th ribs on the right side (Case PO56).

Case 2. A man, aged 20, had tricuspid atresia but only moderate disability as he could walk a mile at his own pace. He had a left-sided anastomosis in 1948. After nine years he is working as a warehouseman and on a recent holiday walked twelve miles—one of the best results I have seen in tricuspid atresia. His small heart has not increased any more than usual (c.t.r. from 40 to 45% one month after operation and 44% nine years after). He still has some cyanosis and clubbing of the fingers and the hæmoglobin has not fallen greatly and is about 130 per cent.

In his case there is less collateral circulation visible over the chest but there is deep rib-notching of the 8th left rib and less obviously of some others (Fig. 2B). In retrospect, this could be seen in the X-ray of 1951 (Fig. 2A) but not in that of 1949, the year after his operation. We are indebted to Dr. W. Whitaker of Leeds for seeing him again and sending us the last X-ray film (Case O278).

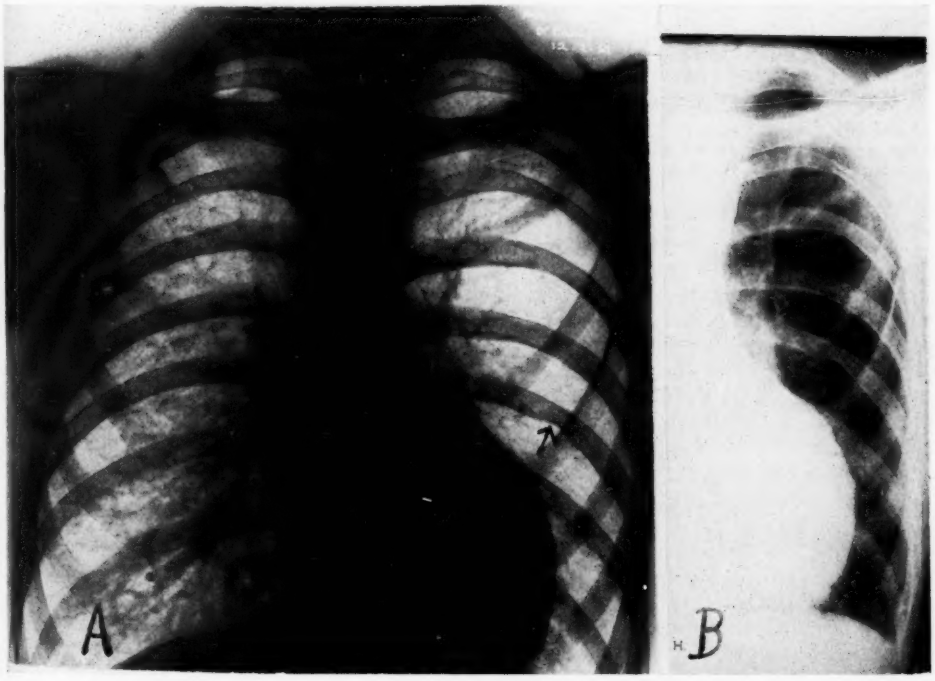


FIG. 2.—Case 2. Unilateral rib-notching, mainly of the 8th left rib after left-sided subclavian-pulmonary anastomosis for tricuspid atresia. (A) In 1951, (B) in 1957. The heart was small before, and remained so after operation, although this was most successful. The 7th left rib in (A) shows minor changes that we have found alone in many cases (see text).

Case 3. A boy, aged 12, had Fallot's tetralogy and could not walk more than 100 yards. After a left-sided anastomosis in 1948, he improved greatly. In 1951 he was attending school regularly and could walk a mile; he was less cyanosed, and the hæmoglobin had fallen from 148 to 104 per cent. The notching on the 5th left rib was not noted (Fig. 3A).

In 1957 he is still doing well and working as an architect. His heart is larger (c.t.r. 57% from 53% in

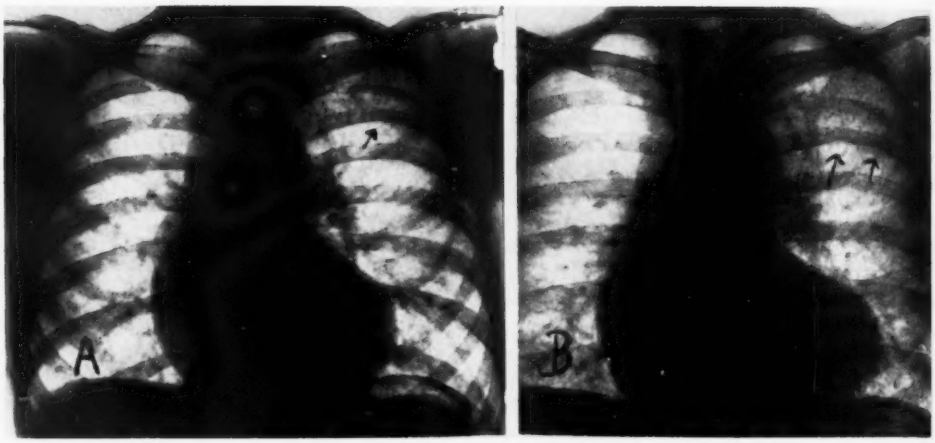


FIG. 3.—Case 3. The development of rib-notching. (A) Four years after a left subclavian-pulmonary anastomosis for Fallot's tetralogy the notches were not detected, but are visible in the 5th left rib below the rib that has regenerated. (B) Five years later the rib-notching is deeper. Incidentally the heart has become somewhat larger (c.t.r. 57% instead of 53%).

1951 and 48% in 1948) and perhaps this may have helped in the detection of the rib-notching at mass radiography but it was also deeper (Fig. 3B). We are indebted to Dr. Posner of Stoke-on-Trent for observing this and for sending us the X-ray film (Case O664).

THE ARM AFTER DIVISION OF THE SUBCLAVIAN ARTERY

A good collateral circulation develops in many parts of the body after loss of the main blood supply. This is so in the arm after division of the subclavian artery, and any significant trouble after a Blalock operation is rare. For a month or two the arm may be rather colder than usual and the patient may be disinclined to use it, but more serious troubles are rare though they have been reported. Holling (in Campbell, 1948) found that two weeks after the operation the forearm blood flow per unit volume was reduced, both at rest and with exercise, but after two months (and once after three weeks) there was no difference either at rest or with exercise. Generally the clubbing of the finger improves equally in both hands but occasionally more so on the side where the subclavian has been divided, suggesting that in these cases the flow may not have returned to a normal level (Campbell and Deuchar, 1953).

A few months after a Blalock operation, most patients are unaware of anything being different in the arm on the side of the operation, though even after eight or nine years I have seen two or three who find it a little weaker than the other, and rarely it is a little smaller. The radial and brachial pulses do not become nearly as strong as before, and up to four years after operation Campbell and Deuchar (1953) were unable to measure the blood pressure by auscultation in the arm on the side of the operation in any patient. As the years pass it is possible to measure the systolic pressure by palpation more often but very rarely the systolic and diastolic pressures by auscultation, though after nine years I have obtained readings that agreed with those in the other arm in one patient and were only 20 mm. below them in one other.

THE COLLATERAL CIRCULATION TO THE ARM

(*a*) *After Division of the Third Part of the Subclavian Artery.* A century ago when peripheral aneurysms were common, division of a subclavian or other large peripheral artery was practised more frequently. Astley Cooper, famous for his contributions to arterial surgery (Brock, 1952), was deeply interested in the collateral circulation. I wondered if these early accounts would include any reference to the intercostal arteries. The first number of the Guy's Hospital Reports

in 1836 contains papers on the circulation that had developed several years after Astley Cooper had ligated the external iliac and common carotid arteries for peripheral aneurysms. There is also an excellent account by Key (1836) of the collateral arteries that were found at necropsy in a man who had undergone an operation for an axillary aneurysm twelve years before.

In such operations the branches of the subclavian are available as a main "providing" source for the collateral circulation. Even so, Key's illustrations show that the collateral arteries extended a long way down the chest wall, certainly as far as the fifth rib. The main anastomosing arteries were (1) posteriorly, from the suprascapular and posterior scapular (from the thyro-cervical) to the infrascapular and so to the axillary artery; (2) internally, from the internal mammary to the short (superior) thoracic, long (lateral) thoracic, and infrascapular (subscapular) arteries, and so to the axillary artery; and (3) smaller but very tortuous branches in the axilla.

Atkins and Joseph (1955) have investigated the collateral circulation in a man who died nineteen years after the right subclavian had been ligated for hæmorrhage; their findings, which were confirmed by radiograms of the injected collaterals, were very similar.

(*b*) *After Division of the First Part of the Subclavian and its Branches.* The position after a Blalock operation is different, for the subclavian is divided nearer to its origin and the branches from the first part—the vertebral, the internal mammary, the thyro-cervical, and generally the costo-cervical arteries—have to be ligated and divided to provide an adequate length of subclavian for the anastomosis, since the free portion of the first part is generally no more than one inch (2·5 cm.) in length and often only half this, even in an adult. The branches cannot, therefore, help directly with the collateral circulation, though they may do so indirectly if they develop fresh anastomotic connections at their proximal ends beyond the division.

Sir Russell Brock has generally found division of all these branches necessary and at operations carried out in 1948 this was almost certainly the case. He has kindly looked up his operation notes and finds that in Case 1 all these branches were divided, in Case 2 the vertebral artery certainly and probably the other branches, and in Case 3 the subclavian was divided just beyond the vertebral and internal mammary which were almost certainly ligated.

When, as is usual, none of these branches is available, the collateral circulation can arise only from (*a*) branches of the aorta, (*b*) branches of the carotid, and (*c*) arteries from the other side of the body. One important route is from the aortic intercostals to the anterior intercostals and so to the internal mammary, and by its anastomoses in the chest wall to the superior thoracic, lateral thoracic, and subscapular branches of the axillary artery. This would, of course, explain the presence of large tortuous intercostal arteries and the consequent rib-notching in one side. I regret that I have missed several opportunities of examining the collateral circulation after injection at necropsy and this should be done.

Webb and Burford (1952), reporting one of the rare cases where the arm had become gangrenous after an operation discussed also anastomoses from the superior thyroid, occipital, and muscular branches of the external carotid to the inferior thyroid, suprascapular, and transverse cervical arteries, and so through anastomoses round the shoulder to the subscapular and other branches of the axillary artery. They give a useful diagram of the possible sources of the collateral circulation. Incidentally, they stated that in this case all the branches of the subclavian had been divided though generally they had not found this necessary.

(*c*) *From the Arm in Coarctation of the Aorta.* Bramwell and Jones (1941) gave an excellent account of the collateral circulation in coarctation. If the vertebral, internal mammary, thyro-cervical, and casto-cervical arteries have been rendered useless for the collateral circulation, the only remaining channels in their list available to function in a reverse direction would be between the lateral and dorsal branches of the aortic intercostals on the one hand and the subscapular, superior thoracic, and lateral thoracic branches of the axillary artery on the other hand.

The Frequency of Unilateral Rib-Notching

These considerations about the collateral circulation explain why the intercostal arteries may become tortuous enough to produce notching of the ribs. It seemed, in fact, rather surprising that

it was not much more common after subclavian-pulmonary anastomosis. Until recently I thought it could not be common, for hundreds of films that had been examined by myself and many others, including radiologists, had revealed only these three cases.

When most of this paper was written, I examined with special care, 16 consecutive cases that had a subclavian-pulmonary anastomosis more than eight years before. There was no case with unequivocal rib-notching that had been missed, but many showed some slight irregularity of the lower border of one or more ribs, always on one side only, that might have been due to a large intercostal artery. Having recognized this possibility, I re-examined the same films a day or two later and now marked 9 of the 16 as showing slight unilateral rib-notching.

Dr. Dow kindly examined these independently and was even more certain that several of them showed unilateral rib-notching: he rejected one of mine but added one I had rejected, so that evidence of it was seen by both of us in 8 and by each of us in one other, making 10 altogether. In all these 10 the side on which we had seen the irregularity of the lower rib margin was found to be the side on which the subclavian had been divided. This convinced us that what we had seen was due to one or more enlarged tortuous intercostal arteries confined to one side, and that a minor degree of unilateral rib-notching is quite common after a subclavian-pulmonary anastomosis. The changes are so small that they are difficult to show in illustrations but perhaps the 7th left rib in Fig. 2A, the rib above the one with obvious rib-notching, gives an idea of the roughened lower rib margin that we are discussing.

Unilateral Rib-Notching in General

(*a*) *In Coarctation.* This condition is well-known and occurs when the left subclavian artery is involved in the coarctation or arises below instead of above it. The blood pressure in the left subclavian is then low, so that there would be less advantage in an anastomosis between it and the lower part of the body, and the anastomosis develops on the right side only. King (1937) reviewed fifteen such cases and added some of his own, but the case of Bayley and Holoubek (1940) was apparently the first in which unilateral rib-notching was seen. Campbell and Baylis (1956) reported two examples among their 130 cases of coarctation and one was illustrated in their Fig. 6A. MacLaughlin (1951), reporting another case where there was also notching of one scapula, discussed the causes of unilateral rib-notching without including any example of the type described by Kent (1953) and in this paper.

(*b*) *In Fallot's Tetralogy and Morbus Cœruleus.* Rib-notching, generally of slight or moderate extent, has been reported in cases that have had no operation, and often this has been mainly or completely unilateral. Batchelder and Williams (1948) described a case with notching of the 5th to 8th ribs on the left side, associated with Fallot's tetralogy and cystic disease in the left upper lobe: there was no coarctation at necropsy and it was thought to be due to an intercostal and mediastinal anastomosis.

In our series of cases of morbus cœruleus, four have been indexed as having unilateral rib-notching. In the first, a boy aged 10 with Fallot's tetralogy, the notching was deepest on the 5th and 6th right ribs but also visible on the 4th right rib (Fig. 4). Dr. Hills' report on the angiocardiogram was "The arterial supply to the right upper lobe is abnormal and blood appears to reach this region from branches of the right subclavian artery". Certainly these branches filled about the same time as the subclavian and probably came from a superior intercostal that had more anastomoses than the usual ones with the first and second aortic intercostal arteries. Even in the patient just quoted without Fallot's tetralogy, Atkins and Joseph (1955) found two branches from the subclavian passing into the lung tissue itself. Our patient had a successful subclavian-pulmonary anastomosis on the left side and no evidence of coarctation was found.

In the second, a man, aged 30, with Fallot's tetralogy, large tortuous intercostal arteries were seen in the upper left interspaces below the rib-notching. At the age of 10 fluid had been removed from his left pleural cavity and he maintained that he had been less cyanosed and less disabled since then. Part of his angiocardiogram at 4 seconds was reproduced by Lowe (1953, Fig. 6).

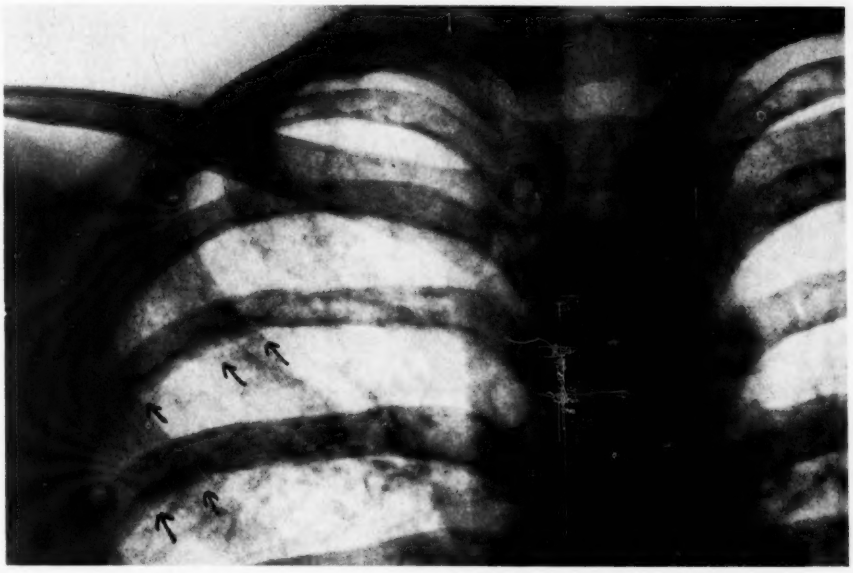


FIG. 4.—Unilateral rib-notching on the 4th rib and deeper on the 5th and 6th right ribs, in a boy, aged 10, with Fallot's tetralogy, before operation. Angiocardiography, showed unusual filling of the right upper part of the lung, which seemed to come partly from the subclavian artery.

In the third, a woman, aged 35, who was thought to have Ebstein's disease, there was notching of three of the upper right ribs (Fig. 1A, Reynolds, 1950). In the fourth, a girl, aged 16, the diagnosis was pulmonary atresia (or possibly truncus arteriosus) and there was a right-sided aortic arch and a continuous murmur that was maximal on the right side but widely conducted. There was slight notching of the fifth and deep notching of the sixth right ribs (Fig. 5) and perhaps of the seventh and tenth. No other collateral circulation was found, nor any evidence of coarctation.

(*c*) *In other Conditions.* McCord and Bavendam (1952) reported one case in which the rib-notching was due to intercostal veins that had become dilated and tortuous from long-standing obstruction of the superior vena cava by a mediastinal mass. Although this is generally regarded as very rare, Dr. Dow tells me that he has seen two such cases, associated with thrombosis of the subclavian or superior vena cava: the cause of the thrombosis was tuberculous glands in one and was unknown in the other.

SUMMARY AND CONCLUSIONS

We have reported three striking examples of unilateral rib-notching after subclavian-pulmonary anastomosis, two for Fallot's tetralogy and one for tricuspid atresia, all on the side where the subclavian artery has been divided. Though this obvious notching is not common we have given reasons for thinking that a minor degree of it from large intercostal arteries is quite common.

This unilateral rib-notching is due to the collateral circulation to the arm of which the subclavian has been divided. When the first part of the subclavian is divided the branches are not fully available for the collateral circulation. Under these conditions, an important source of the blood supply is from the aortic intercostal arteries to the anterior intercostals and so to the trunk of the internal mammary, and by its anastomoses in the chest wall to the superior thoracic and lateral thoracic branches of the axillary artery.

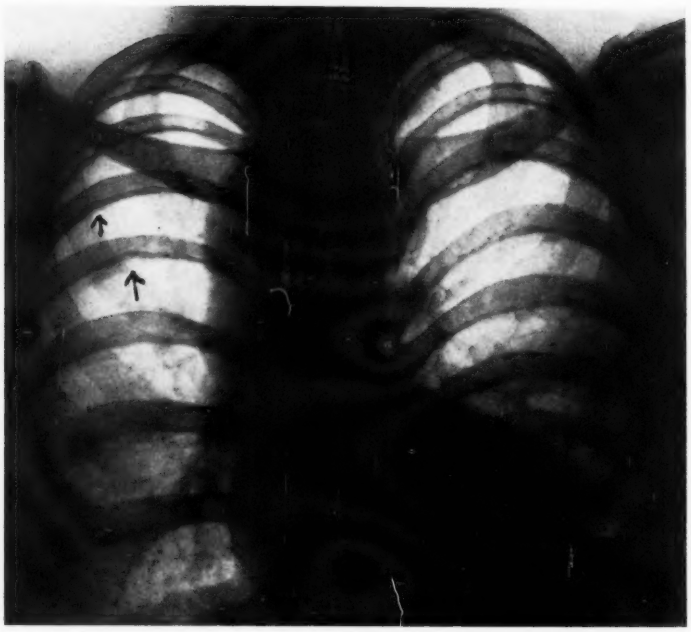


FIG. 5.—Unilateral rib-notching, shallow in the 5th and deep in the 6th right rib. From a girl, aged 16, with pulmonary atresia, who had no evidence of coarctation.

The collateral circulation that develops after subclavian-pulmonary anastomosis is compared with that after division of the third part of the subclavian, an operation that used to be done more frequently a century ago when peripheral aneurysms were common.

Other causes for unilateral rib-notching are discussed shortly.

A fourth striking example with unilateral notching of the 3rd and 4th left ribs has been seen since this was written.

I would like to thank Dr. J. D. Dow for his help and also for examining these radiograms, and Sir Russell Brock, whose surgical treatment has made these observations possible. I am indebted to Dr. Curtis Bain who drew my attention to the first of these cases, to Dr. W. Whitaker and Dr. E. Posner who let me have recent films of Cases 2 and 3, and to Mr. Engel of the Photographic Dept., Guy's Hospital, for the photographs.

REFERENCES

Atkins, H. J. B., and Joseph, J. (1955). *Guy's Hosp. Rep.*, **104**, 380.
Barrett, N. R., and Daley, R. (1949). *Brit. med. J.*, **1**, 699.
Batchelder, P., and Williams, R. J. (1948). *Radiology*, **51**, 826.
Bayley, R. H., and Holoubek, J. E. (1940). *Brit. Heart J.*, **2**, 208.
Bramwell, C., and Jones, A. M. (1941). *Brit. Heart J.*, **3**, 205.
Brock, R. C. (1952). *The Life and Work of Astley Cooper*. E. & S. Livingstone, Edinburgh and London.
Campbell, M. (1948). *Guy's Hosp. Rep.*, **97**, 1.
——, and Baylis, J. H. (1956). *Brit. Heart J.*, **18**, 485.
Campbell, M., and Deuchar, D. (1953). *Brit. med. J.*, **1**, 340.
Kent, J. V. (1953). *Brit. J. Radiol.*, **26**, 346
Key, A. (1836). *Guy's Hosp. Rep.*, **1**, 59.
King, J. T. (1937). *Ann. intern. Med.*, **10**, 1802.
Lowe, J. B. (1953). *Brit. Heart J.*, **15**, 319.
McCord, M. C., and Bavendam, F. A. (1952). *Amer. J. Roentgenol.*, **67**, 405.
MacLaughlin, J. P. (1951). *Brit. J. Radiol.*, **24**, 688.
Reynolds, G. (1950). *Guy's Hosp. Rep.*, **99**, 276.
Webb, W. H., and Burford, T. H. (1952). *J. Thorac. Surg.*, **23**, 199.

SYMPOSIUM ON CONGENITAL HEART DISEASE

As part of the commemoration of the Centenary of the National Heart Hospital, the Institute of Cardiology arranged a symposium on some aspects of congenital heart disease. The subjects chosen were limited to specific problems of current interest, and the opening speakers were asked to limit their remarks to these, without making any attempt to cover the subject as a whole.

The meeting was held at the Ciba Foundation, Portland Place, on Thursday, October 3, 1957. Mr. Wolstenholme, the Director of the Ciba Foundation, said how pleased they were to be able to provide facilities for the meeting. Maurice Campbell thanked him and the Foundation for their hospitality and welcomed the visitors who had been invited to take part in the discussion.

FIRST SESSION *CHAIRMAN: MAURICE CAMPBELL*

Coarctation of the Aorta. The Causes of Heart Failure in Infancy and the Relationship to Fibro-Elastosis

Opened by R. E. Bonham-Carter

Coarctation of the aorta of the adult type presenting as the main lesion accounts for about 4 per cent of all congenital heart lesions at Great Ormond Street. It accounts for 4 per cent of the deaths in the necropsy series. Two-thirds of the deaths from these malformations occur under the age of six months. We have no evidence that coarctation results in heart failure more frequently than other surgically correctable lesions in early infancy.

There are three main reasons why infants with congenital heart disease die so young. The first is their relative lack of immunity to respiratory infection and these tip them over into failure: their inherited immunity declines in the first six months, the measurable decline being in γ globulin and diphtheria anti-toxin levels. The second is the normal depletion of their iron store; this is more obvious in the polycythæmic cyanotic patients, who need to make so many red cells for oxygen transport, but occurs in the acyanotic group also and gives rise to an anæmic anoxia of the myocardium. Clearly, the third reason is the severity of the lesion.

In our series we have a higher proportion of patients complicated by a patent ductus (25%) than would be expected from the published figures (10%). The patency of the duct may delay the essential development of the collateral circulation. Four years ago by doing left auricular biopsy in these and other infants we thought we had found a high proportion with endocardial fibro-elastosis. Reassessment of these biopsies and the post-mortem specimens has shown us that this thickened endocardium is a stress phenomenon and does not indicate the more generalized disease. Serious fibro-elastosis of the left heart is so rare in these infants that the possibility of its presence should not deter anyone from advising resection.

C. G. Parsons. An analysis of 50 cases of coarctation presenting during the first year of life did not suggest that fibro-elastosis was an important factor. The coarctation was post-ductal in 11, of whom 6 survived, and preductal in 39 of whom 38 died; only one had a closed ductus arteriosus. Pneumonia was common and might have been responsible for some deaths but heart failure was usual. Strain on the right ventricle was increased because it was forced to work against a systemic pressure, the ductus being open in all but one infant. Further, there were indications that the pulmonary circulation was abnormal, often with X-ray evidence of pulmonary vascular congestion. Dr. Cameron had found thickening of the media and prominent internal and external elastic laminæ more often in these cases than in normal controls.

R. M. Marquis. In nine cases of coarctation coming to autopsy in the Edinburgh Children's Hospital, endocardial fibro-elastosis has been so common and so variable that we have reached the conclusion that, even when obvious T wave changes are present, it should be ignored in assessing such an infant for surgical treatment.

J. D. Hay. Of nine infants with coarctation, four died, and in none of these was endocardial fibro-elastosis found.

D. J. Waterston. Fibro-elastosis is a post-mortem diagnosis that need not be considered in assessing patients with coarctation for surgery.

R. H. Hudson. Some degree of fibro-elastosis is common in all hearts at autopsy and the condition may be due to organization of blood clot.

R. E. Bonham-Carter (*in reply*). The decision to operate on coarctation of the aorta in infancy depends on the skill of the surgical team. With increasing experience more cases will come to surgery in infancy. At present in my experience the mortality of medical and surgical treatment in infancy is about the same.

COARCTATION: COMPLICATIONS OF RESECTION

OPENED BY GRAHAM HAYWARD

I propose to discuss the vascular lesions found in association with coarctation of the aorta, as these may be important both in the selection of cases for surgical treatment and as a cause of post-operative complications. Some patients, following resection of the coarctation, have attacks of abdominal pain, sometimes associated with vomiting or signs of intestinal obstruction. These symptoms have been shown to be due to an acute arteriolar necrosis, histologically identical with the picture of polyarteritis nodosa. In a recent case laparotomy showed widespread miliary aneurysms, one of which had ruptured and caused massive intraperitoneal hæmorrhage, and another had thrombosed and caused gangrene of a part of the small bowel: episodes of abdominal pain and intestinal obstruction continued to occur for several months after operation. The arteriolar necrosis is said to be caused by the sudden rise in pressure in vessels below the level of the coarctation, and although the lesions seem to subside after a period of time, there may be a place for the use of corticosteroids to prevent the complications of hæmorrhage or thrombosis.

Two of the common causes of death in coarctation are rupture of the aorta due to dissecting aneurysm and intracranial hæmorrhage from rupture of a congenital intracranial aneurysm. Generally, these complications are *not* associated with an excessively high blood pressure proximal to the coarctation, and one of the sites where dissection may occur is just distal to the coarctation. Histologically there is evidence of medial necrosis of the aorta with arteriolar lesions. Although the dissection is usually fatal, a history of episodes of acute retrosternal pain with radiological evidence of unusual dilatation of the aorta suggests that some healing can occur. In such cases operation may be difficult because of the thin and friable aortic wall.

It is suggested that in patients with coarctation of the aorta there may be a widespread abnormality of the small arteries and that this may be responsible for some of the complications that occur before and after operation.

J. F. Goodwin. In one case of abdominal pain after resection of a coarctation, there was either hæmorrhagic ascites or perforation, presumably associated with arterial lesions in the mesenteric vessels. This may be due to a sudden increase of blood flow to the splanchnic area. In another case an aneurysm developed at the site of resection with disastrous results.

D. J. Waterston. It might be useful to examine the resected specimens histologically as a routine for evidence of medial necrosis.

C. G. Parsons. We have some evidence that the aortic wall is always abnormal in uncomplicated coarctation. This is provided by K. W. Donald and S. Taylor, who demonstrated that the response of the pulse pressure to exercise is abnormal both before and after satisfactory resection. A complication of another kind, observed on three occasions, is recurrence of the coarctation after apparently successful operation.

Subaortic Stenosis: Diagnosis and Treatment

Opened by R. M. Marquis

There have been many misconceptions about the frequency, anatomical variations, and clinical features of subaortic stenosis. Surgical experience, by revealing cases that might otherwise have gone unrecognized, has suggested that subaortic stenosis is less uncommon than had been supposed recently, and that it is commonly isolated and may be as severe as valvular stenosis. Moreover, a few cases have been treated surgically with success, so that its accurate diagnosis and assessment is important.

Precision of *diagnosis* depends on the distinction of subaortic from valvular stenosis. At the present time an absolute distinction depends on (1) direct vision of the subaortic lesion at autopsy or (2) direct vision of a normal aortic valve at open operation for known aortic stenosis. Blind transventricular aortic valvotomy may not distinguish subaortic from valvular stenosis, but possibly intra-aortic palpation of a normal aortic valve in the presence of proved aortic stenosis may prove reliable evidence.

Circumstantial evidence for the diagnosis of subaortic stenosis may be obtained by (1) catheter withdrawal tracings from aorta to left ventricle, and possibly by (2) angiocardiography, but it may prove necessary to inject the contrast medium direct into the left ventricle to obtain sufficient clarity of definition in the subaortic region. The site and distribution of the systolic murmur, the quality of the aortic second sound, the shape of the cardiovascular shadow, and the presence or absence of post-stenotic dilatation of the ascending aorta, when correlated with a confirmed diagnosis of subaortic stenosis, may eventually prove of real help.

Treatment. Severe cases require full assessment for surgical relief of the obstruction. At present this is based on experience of aortic valvotomy in general: in future it must depend on an analysis of the results obtained in subaortic stenosis. This distinction is essential, for it should prove possible to relieve subaortic obstruction without the production of aortic regurgitation. The results of operation may, therefore, be more predictable than they are in valvular stenosis and operation may be justified earlier in the course of the disease.

These two slides (not reproduced here), which show the heart from a 12-year-old girl with subaortic stenosis, demonstrate the massive left ventricular hypertrophy that may result from this lesion in a severe form, and the risk of blind transventricular dilatation of a subaortic obstruction, for in breaking down the obstruction, the ventricular wall was torn and the tear extended into the aorta causing partial detachment of one of the aortic cusps.

Clarity in the *discussion* would probably be best achieved if directed to (1) circumstantial evidence of the diagnosis based on the findings in proved cases of subaortic stenosis, and to (2) the results of operation in proved subaortic stenosis.

If we are able to muster sufficient information within these limits, it should be possible to establish criteria by which a diagnosis of subaortic stenosis can be reached without resort to thoracotomy, to obtain an indication of what may be expected from this type of aortic surgery, and to pave the way to recognition of the true frequency of this form of congenital aortic stenosis.

M. Campbell. Dilatation of the first part of the aorta is suggestive but not decisive of valvular stenosis. In 13 necropsies of congenital aortic stenosis (7 children and 4 adults) only 1 was subvalvular (7%), and in 84 cases of isolated aortic stenosis operated on by Sir Russell Brock 5 (6%) were thought to be subvalvular. Unfortunately, aortic regurgitation may sometimes follow an operation for subvalvular stenosis.

P. Wood. In my series of 9 proved cases of congenital aortic stenosis 4 were subvalvular. Aortic regurgitation is common in both types. In some cases of valve stenosis there may also be infundibular stenosis —a situation with which we are only too familiar in pulmonary stenosis.

W. Somerville. Angiocardiography may help to identify stenosis of the left ventricular outflow tract, if (1) the contrast medium is injected rapidly through a wide-bore catheter into the right atrium or preferably the right ventricle, (2) the pictures are taken in the left lateral position, and (3) the exposures are rapid and numerous enough to show both systole and diastole of the left ventricle.

L. McDonald. I have seen a necropsy at which valvular and true infundibular stenosis co-existed. Such cases may be overlooked if pressure gradients are taken from above and below the valve region, without withdrawal tracings. The latter are, in themselves, often difficult to interpret.

R. V. Gibson. It may be difficult to recognize the level of stenosis even on withdrawal tracings across the aortic valve during left-heart catheterization. The subvalvular stenosis may be so close to the valve that it cannot be identified. The absence of calcification of the aortic valve in a patient over the age of 30 is a point in favour of subaortic stenosis. I have seen a case in which there was functional subvalvular stenosis associated with hypertension, with a pressure gradient approaching 100 mm. Hg: necropsy showed a normal aortic valve and gross hypertrophy and functional stenosis of the left ventricular outflow tract.

R. M. Marquis (*in reply*). It would be convenient if post-stenotic dilatation of the ascending aorta were confined to valvular stenosis, but this is suggestive rather than reliable, as it is in pulmonary stenosis. I have no evidence that muscular hypertrophy itself leads to obstruction of the left ventricular outflow tract as it appears to do on the right side in some cases of pulmonary stenosis. Angiocardiography by selective pressure injection through a Lehman catheter into the right ventricle has not always given clear definition, even in the lateral position, but my experience is restricted to apparatus that allows only two films a second.

Valvular and subaortic stenosis may co-exist and calcification may affect the subaortic as well as the valvular lesion. Even so, it is an attractive suggestion that the absence of calcification in patients over 30 favours subaortic stenosis. It is clear from this discussion that there is still much to be learnt about subaortic stenosis. Left-heart catheterization, left-heart angiocardiography, and further surgical endeavour are likely to play the major roles in increasing our knowledge of this relatively uncommon malformation.

The Diagnosis of Mitral Stenosis in the Presence of Atrial Septal Defect

Opened by J. W. Brown

The association of mitral stenosis and atrial septal defect (A.S.D.) is by no means as common as some have thought. It might be reasonable to expect that in cases of A.S.D. the mitral valve would be hypoplastic for the same reason as the aorta, but there is no confirmation of this in specimens examined. Whether there is a rheumatic history or not, the mitral stenosis is of rheumatic type and the valve has not the appearance that is seen, for example, in the mitral stenosis associated with coarctation. Perhaps 5 per cent or less of cases of A.S.D. have mitral stenosis. A Lutembacher syndrome has not been seen in a child, nor is congenital mitral stenosis particularly associated with an A.S.D.

In the past, more often than not, a diagnosis of Lutembacher's syndrome has been based on a diastolic murmur at the apex and this is bound to be unreliable, for at least a fifth of the cases of acyanotic congenital heart disease have such a murmur in the absence of mitral valvular disease. This diastolic murmur can be explained in a variety of ways and its timing is usually mid-diastolic. In A.S.D. it may perhaps be created at the septal defect itself for the defect is a diaphragm-like orifice intervening between the left and right atria. There are, of course, a number of cases of A.S.D. with mitral stenosis that have all the hall marks of mitral stenosis—a loud first sound, opening snap, and diastolic rumble with presystolic accentuation—and it is the large heart and dilated pulmonary vessels in these cases of apparently true mitral stenosis, often with a paucity of symptoms, that leads to catheter and other investigations to look for the septal defect. On these grounds any clinical series of cases of A.S.D. will always include a very few with mitral stenosis. Unfortunately, in many cases the stethoscopic signs of mitral stenosis may be absent because of the large shunt passing from left to right through the defect and bypassing the valve.

What have conventional methods of examination to offer us as a help in diagnosis? With or without mitral stenosis, an A.S.D. shows in radioscopy a large heart with hypertrophy and dilatation of the right chambers and dilated pulmonary arteries. Excessive pulsation of the pulmonary arteries, not always a hilar dance, is very suggestive of an A.S.D. and helps to differentiate it from mitral stenosis with pulmonary hypertension. In A.S.D. with mitral stenosis the left atrial curve may be slightly increased as part of the general enlargement of the heart, and in some cases there may be obvious left atrial enlargement: in others the left atrium is not enlarged at all. The right

atrium usually shows great enlargement. The electrocardiogram tells us nothing about the presence of mitral stenosis, and the P waves are not always bifid. I think that auricular fibrillation in the thirties with a raised jugular venous pressure in a case with cardiac configuration of A.S.D. is very suggestive of the presence of mitral stenosis. It is stated that mitral stenosis emphasizes every clinical and anatomical change produced by an A.S.D.: it may do so in some cases but not always.

When confronted with an average case that comes labelled as Lutembacher's syndrome from radiological findings, it is most likely to turn out to be mitral stenosis with pulmonary hypertension, or A.S.D. alone. The age group usually seen is from 30–70. If the monomarks of mitral stenosis are present, that is the probable diagnosis. If radioscopy shows increased hilar pulsation, then catheter examination may prove the presence of an A.S.D. It rarely proves the presence of mitral stenosis, but the only sure proof of this is a pressure gradient across the mitral valve or palpation of the valve at the time of repair of a septal defect.

P. Wood. In my experience of 400 operations for mitral stenosis only one patient was found to have an A.S.D.: conversely, in 50 operations for A.S.D., only one (2%) had mitral stenosis—a percentage similar to that in the general population. The combination of a large A.S.D. and severe mitral stenosis is, I think, incompatible with life. Has anyone seen such a case? It is easy to estimate the size of the mitral orifice in cases with A.S.D. because the left atrial pressure can be measured by direct inspection of the neck veins. If the cardiac output is over 3 litres a minute and the jugular venous pressure less than 3 cm., there can be no mitral stenosis. All patients with Lutembacher's syndrome have a raised jugular venous pressure, the left and right atrial pressures being about the same, but it is difficult to distinguish between mitral stenosis and a raised left ventricular diastolic pressure as a cause of this (A.S.D. with high venous pressure).

L. McDonald. A gradient across the mitral valve may be caused by mitral regurgitation as well as by stenosis.

J. F. Goodwin. Calcification of the mitral valve is a useful sign in a patient with an A.S.D., but I agree that this does not necessarily mean stenosis.

A. Leatham. The possibility of distinguishing between mitral and tricuspid diastolic murmurs by phonocardiography should not be forgotten.

W. Somerville. Of 50 cases of A.S.D. treated surgically at the Middlesex Hospital 3 had mild mitral stenosis, the valve admitting about one and a half fingers (2·5 cm.). All three were fibrillating, had a raised venous pressure, a large heart (cardiothoracic ratio over 70%) and a normal pulmonary vascular resistance. In retrospect, there was no feature that would have allowed a confident diagnosis of mitral stenosis before operation.

SECOND SESSION — *CHAIRMAN: PAUL WOOD*

Atrial Septal Defect: Reversed Shunt with Normal Pulmonary Vascular Resistance

Opened by Walter Somerville

This is an uncommon condition characterized by three main features: viz. (1) atrial septal defect (A.S.D.), (2) central cyanosis, and (3) absence of any of the established causes of cyanosis in A.S.D., namely, (*a*) raised pulmonary vascular resistance, (*b*) pulmonary stenosis, (*c*) superior or inferior vena cava entering left atrium, (*d*) pulmonary artery thrombosis, or (*e*) tricuspid stenosis.

Three such patients have been seen at the Middlesex Hospital since 1950, two girls aged 10 and 12, and a boy aged 4 years. In two of them auscultatory and phonocardiographic signs suggested A.S.D. and the cardiogram showed right bundle-branch block, but slight cyanosis was present at rest and increased with exercise: in the third the pulmonary second sound was not heard. Cardiac catheterization showed a left-to-right shunt at atrial level in all three and the left atrium

was entered with ease. Right ventricular and pulmonary arterial pressures and pulmonary vascular resistances were normal. Arterial oxygen saturations were 80–85 per cent at rest. Angiocardiograms were carried out *via* the inferior vena cava in two patients and in one of them, *via* the superior vena cava as well, without explaining the cyanosis.

A possible explanation is increased resistance to right ventricular filling from impaired distensibility due to an endocardial or myocardial factor, for example, fibro-elastosis of the right ventricle. However, pressure curves from right atrium and ventricle do not demonstrate any difficulty in right ventricular diastolic relaxation.

P. Wood. In a further three cases, in spite of right bundle-branch block, the second sound was single or normal, unlike Somerville's cases where it was widely split and fixed. I do not think the cyanosis is due to a low defect for it has been absent in many such cases proved surgically. A similar physiological situation occurs when A.S.D. is associated with either Ebstein's disease or gross pulmonary regurgitation secondary to idiopathic dilatation of the pulmonary artery.

R. V. Gibson. If the A.S.D was closed, the subsequent physiological findings might help to solve the problem.

P. Wood. In a case somewhat similar but with cyanosis developing later, in which the A.S.D. was closed, there was found to be free tricuspid regurgitation and this increased and the jugular venous pressure rose after closure of the A.S.D.

W. Brigden. The cyanosis might be due to left ventricular disease causing a modified Bernheim effect.

J. F. Goodwin. The A.S.D might be high, giving perferential shunting from superior vena cava into left atrium.

M. B. McIlroy. Using ear oximetry it can be shown that a number of cases of A.S.D. desaturate on exercise: this might support the theory of preferential shunting.

R. E. Bonham-Carter. A likely explanation is that the A.S.D. is associated with Ebstein's disease, as in pædiatric practice varying degrees of Ebstein's disease are not uncommon.

W. Evans. In the second case the right ventricular hypertrophy together with right bundle-branch block suggests that there might have been some pulmonary hypertension in spite of the pressures recorded at catheterization. The opener did not agree.

A. Leatham. Could the cyanosis be caused by an abnormally low end-diastolic left ventricular pressure?

W. Somerville (*in reply*). Surgery had been considered in one of our cases but so far has not been done. The possibility of an associated Bernheim effect has been thought of but there was no evidence of left ventricular disease. The possibility of a high A.S.D. accounting for the cyanosis is unlikely as many such cases, confirmed surgically and at necropsy, have been free from cyanosis.

The Cause of the Respiratory Fixation of a Split Second Sound

Opened by Aubrey Leatham

Wood drew attention to obvious splitting of the second heart sound as a physical sign of atrial septal defect (Barber *et al.*, 1950). Phonocardiograms at the London Hospital showed that aortic closure was first and was separated from pulmonary closure by an interval of 0·04 to 0·05 sec. This was no greater than the normal interval during the inspiratory phase of respiration; the abnormality lay in the persistence of the splitting in the expiratory phase of respiration, the split decreasing only very slightly during expiration.

At first this was attributed to delay in onset of electrical activation of the right ventricle as suggested by the rSR′ complex in the electrocardiogram. No delay, however, was found in the onset of the right ventricular pressure pulse (Leatham and Gray, 1956). Prolongation of electrical activation of the right ventricle was a possible cause, but no abnormality of splitting of the second sound was found in patients with a similar electrocardiogram, but without an A.S.D. Selective increase in right ventricular stroke volume (compared with the left, because of the left-to-right shunt) has been thought the most likely cause for the wide splitting of the second sound. A further increase in right ventricular stroke volume on inspiration (as in normal subjects) was perhaps impossible or greatly reduced, so that little further delay in pulmonary closure occurred on inspiration,

thus accounting for the respiratory fixation. The wide fixed splitting was found with high pulmonary vascular resistance also, provided that the left-to-right shunt continued, but was absent when there was a right-to-left shunt that reduced the right ventricular stroke volume. Finally, the abnormal splitting was found to disappear in a few patients in whom the defect had been closed, even when the electrocardiogram was unaltered.

Further experience, however, with the increasing numbers of patients whose defects have now been closed shows that there may be a delay in return of the second sound to normal of several weeks or longer following the operation (Blount, 1954; Wood and Somerville, both personal communications). This challenges the concept of selective increase in right ventricular stroke volume as the cause of the abnormal second sound, and suggests that it may be due to changes in pulmonary vascular resistance. Since the greatly increased flow in uncomplicated A.S.D. is accompanied by normal pressures there must be a decrease in pulmonary vascular resistance. Jonsson (personal communication) points out that the dicrotic incisura is then low down on the descending limb of the pulmonary artery pulse wave, and thus pulmonary closure is late. With a high pulmonary vascular resistance the incisura is situated high up on the descending limb and pulmonary closure is early. There appear to be exceptions to this rule and further study is required, particularly of changes in pulmonary vascular resistance with respiration and their relation to splitting of the second sound.

W. Somerville. The split has been fixed in 70 per cent of the first 50 cases of A.S.D. in which the defect has been closed at the Middlesex Hospital. In a number of these the delay in the pulmonary second sound persisted a year after successful closure of the defect, as proved by catheterization. In nearly all these, the pulmonary resistance was under one unit.

J. Shillingford. Have any observations been made on the behaviour of the aortic second sound after the administration of various drugs that might lower the peripheral resistance?

R. Gibson. In 40 cases of A.S.D. only one had a normally split second sound before operation: there was systemic hypertension and after closure of the defect the split became reversed. In A.S.D. inspiration affects right and left ventricular filling equally, therefore it would be unlikely for the split to widen during this phase of respiration, and the fixed split is not incompatible with the hypothesis that the delay in the pulmonary second sound is caused by increased stroke volume of the right ventricle.

R. E. Bonham-Carter. The pulmonary second sound does in fact move a little with respiration in most cases, especially in children. To this *Leatham* agreed saying it amounted only to 0·01 sec.

P. Wood. I am surprised at Somerville's finding concerning the behaviour of the second heart sound after closure of the defect: in 14 of the last 15 cases in which the defect has been closed the split had become normal 5 to 10 days after operation—the average time being 7 days. The delay in the pulmonary second sound is due to increased stroke volume of the right ventricle, and probably the right ventricular filling resistance may return to normal slowly after operation. During this post-operative phase the split is fixed when the patient is lying, but on sitting, which lowers the venous pressure, the split becomes normal. If this view is correct, the cardiac output should be raised in the immediate post-operative period, a point that is under investigation.

A. Leatham (in reply). I agree with Wood and think the most likely hypothesis is that the delay in the pulmonary second sound is caused by over-filling of the right ventricle.

The Cause of the Continued Left-to-Right Shunt in A.S.D. when the Right Atrial Pressure is High

Opened by Ronald Gibson

In most cases of A.S.D. with a low or moderately raised pulmonary vascular resistance the shunt continues to be wholly or predominantly left-to-right when the right atrial pressure is high: the left atrial pressure remains as high or higher than the right. It follows that, despite the high atrial pressures, the right ventricle must still offer a lower resistance to filling than the left, as is usual in uncomplicated A.S.D. Therefore, the crucial question is what is the mechanism whereby, in the presence of a high atrial pressure, the left ventricle maintains its normal higher resistance to filling?

Three different mechanisms have been postulated: (1) left ventricular filling is limited by tension due to a stretched pericardium, (2) the high atrial pressure is due to left ventricular failure or malfunction of the left ventricle, or (3) left ventricular filling is impaired because the inter-ventricular septum is bulging into the cavity of the left ventricle (reversed Bernheim's syndrome).

(1) The pericardium does not seem to play any part in limiting left ventricular filling, since it is not tense at operation, the heart does not herniate through the incised pericardium, and the left-to-right shunt continues after the pericardium has been opened widely. (2) The evidence that the high atrial pressure is due to left ventricular failure is unconvincing for the alleged failure is attributed to mitral regurgitation or systemic hypertension of a degree that would not ordinarily cause failure. (3) The concept of impaired left ventricular filling due to bulging of the septum to the left is interesting but difficult to prove. None of these mechanisms offers a wholly satisfactory explanation for the continued left-to-right shunt, although the reversed Bernheim's syndrome is the least objectionable.

The high atrial pressure is a manifestation of right ventricular failure, and the continued left-to-right shunt is due to the right ventricle in failure remaining more readily distensible than a normal left ventricle (if the left ventricle can be regarded as normal in A.S.D.). The different atrial and ventricular end-diastolic pressure levels in right and left heart failure offer some support for this view. In right ventricular failure from any cause they are usually 10–15 mm. Hg (identical with the pressures found in the type of A.S.D. under consideration). By contrast, in left ventricular failure they are usually much higher at 30–40 mm. (personal observations at thoracotomy in eight cases, seven with aortic stenosis and one with ischæmic heart disease, all of which were in left ventricular failure at the time). The level of the atrial or ventricular end-diastolic pressure in this type of A.S.D. would not be high enough to influence materially left ventricular filling and the right ventricle would remain more readily distensible than the left, even though the former is in a state of failure. If this were so then clearly the shunt would continue to be wholly or predominantly left-to-right despite the high right atrial pressure.

W. P. Cleland. The pericardium at operation is always slack in these cases and never constricting.

J. Shillingford. Left ventricular end-diastolic pressure in failure is surprisingly high, 20 mm. Hg at rest and 30–40 mm. on exercise.

L. McDonald. There is no need for it to be raised to the levels found with clinical heart failure: smaller increases might indicate ventricular dysfunction.

P. Wood. In 22 cases of A.S.D. with raised jugular venous pressure, a left-sided lesion or increased output has been found in 19 (11 had hypertension with a diastolic pressure over 120 mm. Hg, 5 had mitral valve disease, 2 were thyrotoxic, and 1 severely anæmic): this, however, does not explain the 3 others. But essentially these findings support the views of Dexter (1956).

M. B. McIlroy. If the venous pressure is reduced by tipping the patient, there is difficulty in left ventricular filling, manifested by a fall in systemic pulse pressure.

R. E. Bonham-Carter. V.S.D. is a common cause of failure in infancy and in these cases the shunt remains left-to-right: this supports the view that ventricular filling is at fault.

R. Gibson (in reply). I disagree with the theory that a left-sided lesion is important. I have seen a case where the venous pressure had been raised for 7 years, and if this was due to left ventricular failure the patient would have been unlikely to survive so long.

P. Wood. The problem is largely a matter of nomenclature: the filling resistance to the left ventricle is raised, but the cause for this is still uncertain.

The Significance of a Pressure Gradient across the Pulmonary Valve in A.S.D.

Opened by Lawson McDonald

Interest in the significance of the systolic pressure gradient across the pulmonary valve which occurs not uncommonly in A.S.D., has heightened with the now excellent results of operative repair of this defect. There are several important questions. Firstly, whether the gradient indicates true pulmonary stenosis, and if so, whether it is ever severe enough to merit valvotomy at

the time of repair of the A.S.D. Secondly whether the pressure gradient may be produced by some other mechanism than pulmonary stenosis, possibly involving the increased pulmonary blood flow, such as (*a*) disproportion between a pulmonary valve of normal area and increased blood flow through it, (*b*) disproportion between an abnormally large right ventricle and a relatively normal valve ring, (*c*) suction effect on the catheter tip, or (*d*) functional obstructions occurring in the outflow tract of the right ventricle, or a combination of such mechanisms.

With these points in view I have analysed the hæmodynamic findings on 50 consecutive cases of A.S.D., all ostium secundum defects; a large number have already had the defect repaired by Sir Russell Brock. In Fig. 1 the pulmonary systemic flow ratio (pulmonary flow divided by systemic

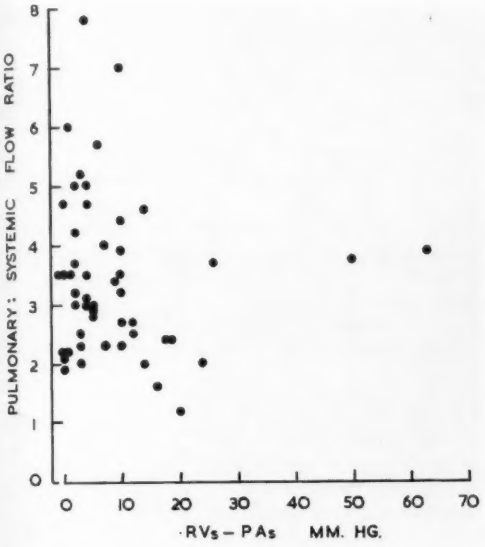


FIG. 1.—The relationship of the pulmonary/systemic flow ratio (pulmonary flow in l./min. divided by systemic flow in l./min.) and the pulmonary systolic gradient (right ventricular systolic pressure minus pulmonary arterial systolic pressure in mm. Hg) in atrial septal defect. See text.

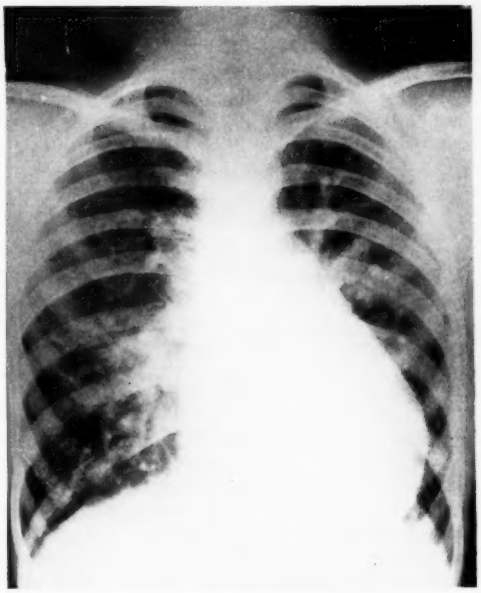


FIG. 2.—X-ray of the chest in a patient with atrial septal defect and a pulmonary systolic gradient of more than 60 mm. See text.

flow, both in l./min.) is related to the systolic gradient across the pulmonary valve (RV–PA in mm. Hg). The error in estimating pulmonary blood flow by the Fick principle, in the presence of left-to-right shunts, is of course well-recognized. But even taking this into account, the highest gradients (including one of 63 mm. and another of 50 mm.) occurred not in the cases with the greatest pulmonary flows, but in those with only moderately increased flows (pulmonary systemic flow ratios of 3–4/1). This suggests that the magnitude of pulmonary blood flow, although it may affect the systolic gradient, is not the main factor in determining it. Alternatively, some degree of pulmonary stenosis may prevent the extreme increases of pulmonary blood flow in A.S.D. But in pulmonary stenosis with an intact septum needing valvotomy, the pulmonary arterial mean pressure is not well maintained, and the arterio-venous oxygen difference becomes exaggerated.

Fortunately operative findings illuminate the problem. It is already proven that these systolic pressure gradients across the pulmonary valve in A.S.D. may disappear after closure of the defect. This occurred in the patient with the gradient of 63 mm., and Blount of Denver has written to me of a patient with atrial septal defect and a systolic gradient of 78 mm. across the pulmonary valve, which was found to be zero at catheterization after operative repair of the defect. This is an extreme example of a type of case of which we have growing experience, where even a towering gradient is unaccompanied by pulmonary stenosis, and therefore indicates the unreliability of the gradient as a sole guide. Sir Russell Brock tells me that, although he has closed an A.S.D. during an operation performed for pulmonary stenosis, he has never found pulmonary stenosis that he considered in need of valvotomy, at the time of operation undertaken for the repair of A.S.D. I am aware that all surgeons will not concur with this.

It seems, in conclusion, that pulmonary stenosis requiring surgical relief is unlikely, or possibly even incompatible, with the hæmodynamic changes occurring in A.S.D. cases needing repair. Fig. 2 shows the X-ray of the chest of a patient with a pulmonary systolic gradient of more than 60 mm.: it is hard to conceive that the pulmonary valve is in any way damming back the flow of blood into such plethoric lungs. This is not so say that the pulmonary valve is necessarily normal with A.S.D., but that any apparent obstruction at the pulmonary valve should perhaps best be reassessed after operation, as I believe that even if any true stenosis is present it will seldom, if ever, merit surgical correction in these cases.

M. B. McIlroy. I have been able to record a gradient at two different heart rates: with sinus rhythm of 95 a minute the gradient was 38 mm. and with flutter at 130 it fell to 25 mm. Hg. The stroke volume had fallen from 270 ml. with sinus rhythm to 170 ml. with flutter.

P. Wood. I agree with McDonald that there is no direct relationship between the flow and the gradient (slide shown). Some of the gradient is artifactual as it can not always be confirmed at operation, or when the pulmonary arterial pressure is checked by wedging the catheter in a pulmonary vein.

W. Somerville. A pressure gradient (range: 3–26 mm. Hg) across the pulmonary valve was present in half of our first 50 cases where an A.S.D. was closed. No correlation was found between the size of the gradient and the pulmonary flow, the left-to-right shunt, or the heart size.

M. Campbell. I have seen 16 patients with A.S.D. and a gradient of more than 20 mm. Hg across the pulmonary valve. (1) 10 had large shunts up to 14 litres and gradients between 20 and 40 mm. (2) 3 had similar shunts and gradients between 70 and 90 mm. (3) The last 3 are hardly pertinent as they had similar large gradients but shunts of about 1 litre a minute that may become reversed. The smallest gradient where pulmonary stenosis was proved at necropsy was 35 mm. in a case of V.S.D. Though moderate-sized gradients may be due to a Venturi effect, we think that gradients of more than 35, or perhaps 45 mm., generally indicate slight stenosis or some narrowing in a dilated tract; and that if the flow is normal or only slightly increased, even smaller gradients such as 20 mm. may indicate slight stenosis (see Brotmacher and Campbell, 1958).

W. Brigden. The answer could probably be supplied by a hydrodynamic physicist.

J. Shillingford. Recent work from our laboratory by Hoffman showed that, with a large pulmonary artery and no stenosis, the Venturi effect alone could account for a gradient of 15–20 mm. Another factor is the angle of the aperture in the catheter to the flow, and to a lesser extent the site of the aperture in the catheter, i.e. tip or side. With a flow of 5 litres there might be a 5–10 mm. gradient and this gradient increases by the square of the rise in the flow.

J. F. Goodwin. Why is a gradient not found in all cases?

L. McDonald (in reply). The "functional" gradient seems to be something peculiar to A.S.D. and similar gradients may not occur with V.S.D.

The Diagnosis of Persistent Ostium Primum

Opened by Patrick Mounsey

Recent advances in the surgical treatment of A.S.D. have made the differentiation of a persistent ostium primum from a persistent ostium secundum of importance. While defects of the ostium

secundum type have been safely and successfully closed in many centres, closure of an ostium primum presents greater technical difficulties and requires a heart-lung machine.

It is important to define the pathological entity. The ostium primum lesion may be the only abnormality apart from a bifid anterior cusp of the mitral valve, or it may be associated with a single common atrio-ventricular (A-V) valve and a V.S.D., when the condition is known as a persistent atrio-ventricular canal. Intermediate between these two extremes many different gradations of lesions are met. As might be expected the prognosis is better for the least severe type of pathological abnormality.

A generic name is needed to describe all of these lesions and thus differentiate them clinically from the persistent ostium secundum, which has been estimated to be about ten times as common. The names that have been proposed are persistent ostium primum, persistent common (A-V) canal, endocardial cushion defects, and atrio-ventricularis communis. Some of these cover only one type in the group, but the important thing these names try to convey is the basic concept of a gradation of A-V canal defects, resulting from failure of fusion of the endocardial cushions and the septum primum.

The points on which a diagnosis of persistent ostium primum may be suspected clinically have been recently summarized by Blount *et al.* (1956), Brandenburg and DuShane (1956), Bedford *et al.* (1957), and Campbell and Missen (1957). They depend on the frequent association of regurgitation at one or both A-V valves, most frequently the mitral, on the presence of an associated V.S.D. in some patients, and on the large size of the left-to-right shunt usually present.

When there is neither regurgitation at the A-V valves nor an associated V.S.D., the persistent ostium primum is probably clinically indistinguishable from a persistent ostium secundum. Thus, on clinical examination the patient is found to have the physical signs of A.S.D.—a cardiac impulse of right ventricular type, a systolic murmur, and relatively fixed splitting of the pulmonary second sound in the pulmonary area—but in addition there may be a loud pan-systolic murmur and thrill at the apex or the left sternal edge. Radiological findings include right atrial and right ventricular enlargement, dilatation of the pulmonary artery and its main branches, and pulmonary plethora, all typical of a large A.S.D. of the ostium secundum type, but in some patients there is evidence of left ventricular enlargement also.

Catheterization may show evidence of a left-to-right shunt at low atrial levels or at both atrial and ventricular levels; further evidence of the site of the septal defect may be obtained by observation of the path taken by the catheter in passing from the right atrium into the left ventricle. The electrocardiogram may sometimes give a valuable diagnostic clue, since it often shows partial right bundle-branch block with left axis deviation (Toscano–Barbosa *et al.*, 1956). Left ventricular preponderance, left bundle-branch block, and complete heart block have also been reported and it may be that the electrocardiographic pattern seen in persistent ostium primum is related to the nature and severity of the defect of the A-V canal present.

Other points that may suggest the presence of a persistent ostium primum in a patient with an A.S.D. are an unusual degree of cardiac enlargement in childhood, general physical underdevelopment and mongolism, pulmonary hypertension occurring before the age of 20, and bacterial endocarditis, which is rare with the secundum type. Although patients with the most severe types of A-V canal defect die in infancy, those with a less extensive defect may live to 60 (Rokitansky, 1875) and a persistent ostium primum cannot therefore be excluded on age alone.

L. McDonald. These two slides demonstrate a point in catheterization that may help in the differentiation: in the primum defects the catheter may escape easily into the aorta, but not with secundum defect.

J. D. Hay. Fabricius of Copenhagen claims to be able to differentiate these two defects and measure the size of the defect by the range of free movement of the tip of the catheter when it has been looped in the right atrium before being passed through the defect. Has anyone found this useful?

W. Brigden. It is difficult to assess a pansystolic murmur in the presence of an A.S.D. What is the frequency of left ventricular changes in the electrocardiogram of this condition?

A. Leatham. Two cases over 50 years of age with necropsy control had left axis deviation and a late secondary R in aVR.

W. Brigden. Similar changes may be seen in V.S.D.

R. V. Gibson. Left axis deviation is a constant finding, but mitral regurgitation may or may not be present, and the same applies to a shunt direct into the ventricles. Q waves in V5 and V6 may be misleading as they are seen in secundum defects also.

R. M. Marquis. A girl, aged 9, with ostium secundum and with necropsy control had left axis deviation: there was no systemic hypertension in this case, and the intensity of the signs led to a diagnosis of V.S.D.

L. McDonald. In recent work (Hamer, 1958) at the Institute of Cardiology, left axis deviation appeared almost as reliable a sign of ostium primum as the abnormal vectorcardiogram, but there were three cases without it.

J. D. Hay. The cardiographic changes may be less at birth and may develop with increasing years.

P. Wood. Keith described a number of cases in infants under two years old who had left axis deviation.

C. G. Parsons. I agree that these changes may develop later. Left axis deviation may signify a common A-V canal, and we have seen cases of ostium primum without it. When flow through the defect is reversed, a few of our cases suggest that angiocardiography may distinguish between these lesions: with an ostium secundum blood is directed towards the roof of the left atrium; with an ostium primum it passes in an explosive manner towards the posterior wall of the left atrium.

Anomalous Pulmonary Venous Drainage

Opened by Dr. J. F. Goodwin

I should like first to consider the diagnosis of partial anomalous venous drainage with A.S.D. The anomalous vein or veins may be visible on the plain X-ray, and the cardiac catheter may enter a vein from the right atrium, in which case the diagnosis presents no problem (Fig. 3). Brewer (1953) has suggested that the right pulmonary artery may be small in cases of right pulmonary veins draining into the right atrium, but this has not been my experience.

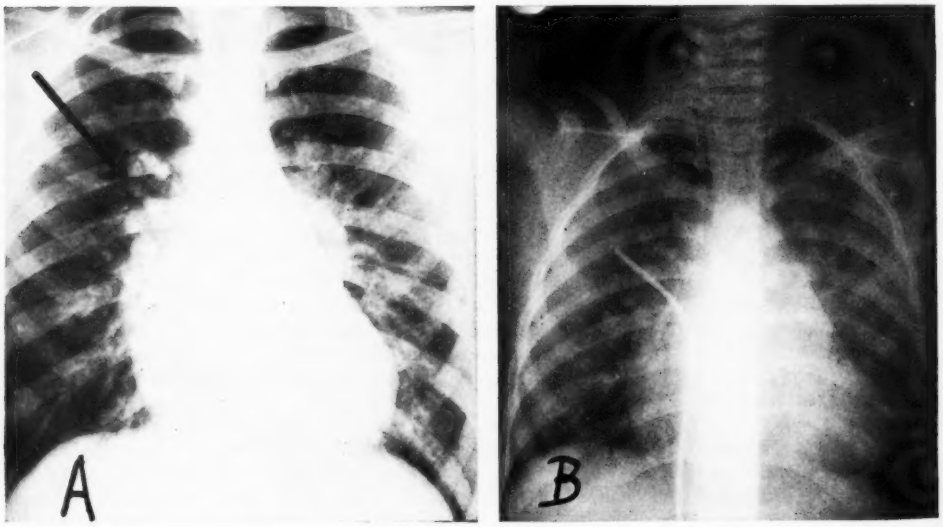


Fig. 3.—P-A tele-radiograph of a child with anomalous right pulmonary veins and atrial septal defect. (A) The upper anomalous vein (arrowed) can be seen as it enters the upper part of the right atrium. (B) Cardiac catheter entering the anomalous vein from the right atrium.

Anomalous pulmonary veins, however, may enter the right atrium at an unusual site and be associated with anomalous caval drainage. In a personal case the right pulmonary veins entered the roof of the right atrium, and the inferior vena cava entered the left atrium (Fig. 4). This situa-

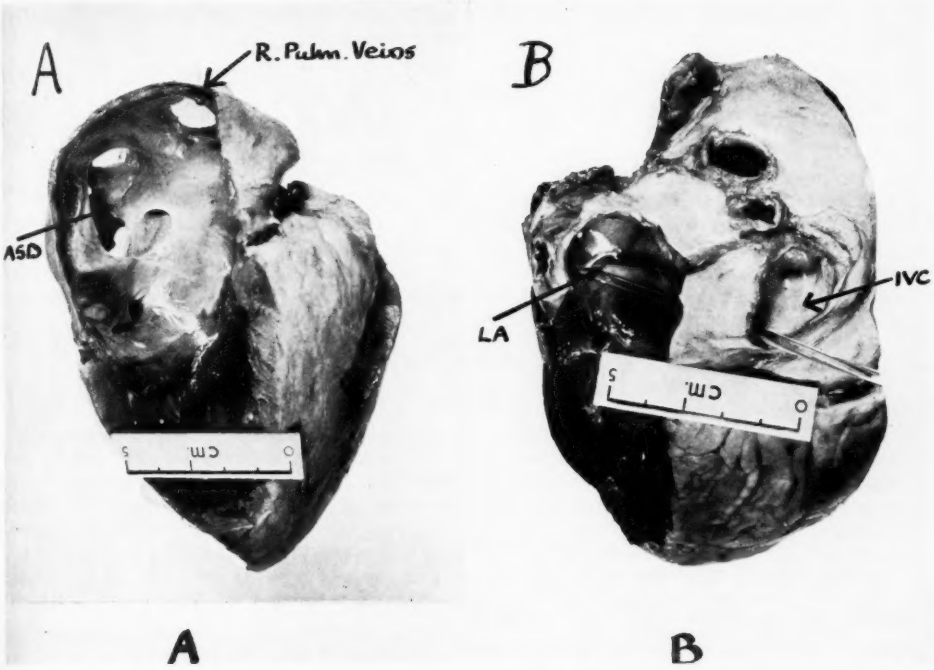


FIG. 4.—(A) Anterior view of the heart of patient with atrial septal defect and anomalous pulmonary and caval venous drainage. The pulmonary veins from the right lung enter the roof of the right atrium (arrowed). The fenestrated septal defect (A.S.D.) is well shown. (B) Posterior view. A glass rod passes through the inferior vena cava (I.V.C.) which enters the left atrium (L.A.).

tion is very dfficult to diagnose, and I should like to ask the surgeons present how much embarrassment anomalous venous drainage is likely to cause during an operation for closure of an A.S.D. A high A.S.D. involving tissue postero-superior to the fossa ovalis tends to be associated with anomalous pulmonary veins, and the superior vena cava may override the septum causing slight right-to-left shunting. Dye dilution techniques have shown preferential shunting from right to left of superior caval as opposed to inferior caval blood (Swan *et al.*, 1957).

I should now like to consider the diagnosis of partial anomalous venous drainage without A.S.D. I have never diagnosed such a case. I should like to know whether the physical signs and the electrocardiogram are the same as in A.S.D. Obviously, the differential diagnosis from A.S.D. is of the greatest importance. The detection of any right-to-left shunt by dye dilution techniques would presumably indicate the presence of an inter-atrial communication (Swan *et al.*, 1953). Alternatively, if differential dye studies from each lung showed a left-to-right shunt from one lung only, this might give the answer. Selective pulmonary arteriography in two planes might also afford the solution.

Finally, I wish to consider the prognosis of total anomalous venous drainage with special reference to size of the inter-atrial defect, and the presence of obstructive pulmonary hypertension. Presumably, survival depends upon the size of the A.S.D., and early death may be associated with

a very small defect. Obstructive hypertension would tend to increase the right-to-left shunt at atrial level. This might impair the function of a hypoplastic left ventricle and produce left ventricular failure, although this might well be prevented by restriction of inflow from the pulmonary veins. Two patients in my series are only moderately incapacitated although having considerable pulmonary hypertension. I should like to provoke discussion on whether some degree of elevation of pulmonary resistance may not actually help these patients.

W. Somerville. An angiocardiogram may demonstrate anomalous pulmonary veins draining into the right atrium. The medium should be injected *via* a catheter placed in the right ventricle or pulmonary artery and late opacification of the right atrium from pulmonary veins may be seen in the postero-anterior and/or lateral planes. However, an associated large left-to-right shunt through an A.S.D. may obscure the details of right atrial opacification.

J. Shillingford. Swan uses dye curves to differentiate between pulmonary veins draining into right and left atria by injecting dye into the anomalous veins and noting the appearance time at the periphery and the shape of the curve.

W. P. Cleland. The anatomy is important. If the veins enter near the septum they can be excluded from the right atrium when the septum is repaired, but unfortunately, this only applies to a small group. In cases where the veins enter further away from the septum more time is needed for restoration of the normal anatomy and an extra-corporeal circulation is necessary. Tomography may help to determine the exact anatomy, particularly in cases where the veins enter the right atrial border.

J. D. Hay. We have seen four fatal cases of total anomalous pulmonary venous drainage in 128 infants with congenital heart disease. Maude Abbott found only four in 1000 autopsies on patients of all ages. This suggests a high death rate from this condition in the early years of life and the need for early treatment.

Arnold Johnson (of Montreal). In four cases with total anomalous venous drainage of the lungs, the veins drained below the diaphragm and entered the left portal vein and ductus venosus. One was diagnosed during life by angiocardiography. Histological changes in the lungs of these cases were similar to those seen in mitral stenosis.

D. J. Waterston. Most of these cases must come to operation and the exact anatomy can best be determined at thoracotomy. When the veins enter high up near the mouth of the superior vena cava there is always a danger of narrowing the caval orifice if an attempt is made to repair the anomaly: it is preferable to ligate these veins and do a right upper lobe lobectomy.

P. Wood. High veins into the superior vena cava are often associated with a small defect and therefore the shunt from the veins may be the more important factor. I agree with Somerville about the difficulty of clinical diagnosis in cases of total anomalous pulmonary veins from one lung and no A.S.D. Is the degree of plethora in the two lungs the same in this condition?

J. F. Goodwin (in reply). I find no difference in the two lungs radiologically. Selective angiocardiography into the pulmonary artery may be disappointing in this condition owing to the dilution of dye by the large blood flow.

THIRD SESSION — *CHAIRMAN: WILLIAM EVANS*

Pulmonary Hypertension with Reversed Shunt (Eisenmenger's Syndrome)

(1) The Nature of the High Pulmonary Vascular Resistance

Opened by W. Whitaker

In the time at my disposal I cannot discuss fully the controversial issue of the relative parts played by vascular spasm and structural disease in the pathogenesis of the high pulmonary vascular resistance. I shall confine myself to a description of the histological abnormalities occurring in the small pulmonary blood vessels of patients with severe pulmonary hypertension.

Heath and I have studied many patients with congenital and acquired heart disease and have found a close association between the histological appearances in the small pulmonary blood

vessels and pulmonary arterial pressure. Where the pressures were normal or only slightly raised, the mean being below 50 mm. Hg, the pulmonary blood vessels were normal; but with higher pressures there were structural changes, and with mean pressures of 50 to 70 mm. a media was found in vessels less than 100μ in diameter, which we accepted as pulmonary arterioles. Someone is bound to assert that these small vessels were not arterioles but contracted muscular arteries and it is impossible to deny that vascular spasm could account for the appearance of a media in vessels less than 100μ. However, in patients with more severe degrees of pulmonary hypertension, where the pressures were of the order of the systemic pressures, there was in addition to medial hypertrophy extensive structural changes in the intima. In this group of patients we invariably found medial hypertrophy and proliferation of the intimal tissue in the muscular pulmonary arteries and in the pulmonary arterioles: in many vessels the lumen was obliterated by the proliferated intimal tissue, and I believe that these organic changes are responsible for the high pulmonary vascular resistance in Eisenmenger's syndrome.

Occasionally, but not consistently, other abnormalities were found in the small pulmonary blood vessels of patients with severe pulmonary hypertension. In some there was aplasia of the media, and in others there were dilated branches arising from the muscular pulmonary arteries proximal to their site of obliteration, in others obliterated vessels were recanalized, and occasionally in patients with severe idiopathic pulmonary hypertension arteriolar necrosis was seen.

In conclusion, I would like to make a plea about terminology. It is unfortunate that the term Eisenmenger's syndrome has been coined to describe all cyanosed patients with severe pulmonary hypertension. While I am quite happy to see the diagnosis Eisenmenger's complex preserved in cyanosed patients with ventricular septal defect and pulmonary hypertension, I am offended by such terms as "An Atrial Septal Defect Eisenmenger's Syndrome". Since it is now recognized that cyanosed patients with severe pulmonary hypertension not only present as a clinical entity but also have characteristic pathological features, I would suggest as an appropriate diagnosis in such cases Hypertensive Pulmonary Vascular Disease.

P. Wood. The pulmonary hypertension of Eisenmenger's syndrome is merely a failure of the pulmonary vascular resistance to diminish after birth. These slides illustrate that there is no release of the pulmonary vascular resistance by acetyl choline in the Eisenmenger syndrome as compared with primary pulmonary hypertension. There is thus no functional vasoconstriction in the adult, but the situation may be different in childhood.

M. Campbell. Wood's first remark may be true in P.D.A. with a reversed shunt; it is rarely true in A.S.D., and in V.S.D. many cases have hyperkinetic pulmonary hypertension at first and develop increased pulmonary arteriolar resistance some years later.

J. F. Goodwin. In the adult patient with Eisenmenger's syndrome, hexamethonium fails to produce any change in pulmonary vascular resistance as compared with pulmonary hypertensive mitral stenosis.

Arnold Johnson (of Montreal). The earliest age at which I have seen intimal thickening in the Eisenmenger syndrome in childhood is six years: this suggests that there may be some functional vasoconstriction as well in childhood.

R. E. Bonham-Carter. In cases of patent ductus with pulmonary hypertension, biopsy of the lung, using sections taken a uniform distance from the hilum, has shown regression of arterial change after operation.

William Evans. The vessels that Whittaker has shown on his slides are in fact small arteries that have undergone post-mortem contraction, as shown by the waviness of the internal elastic lamella, rather than arterioles that had developed muscle in their walls. *R. H. Hudson* agreed with Evans.

(2) Identification of the Site of the Shunt in Cases of Reversed Shunts in A.S.D., V.S.D., and P.D.A.

Opened by Wallace Brigden

Recognition of the site of the shunt in Eisenmenger's syndrome is often difficult, even after full clinical and laboratory investigation. Necropsy sometimes proves that it was incorrectly diagnosed

even after elaborate tests. Symptoms such as dyspnœa, effort pain, effort syncope, and hæmoptysis are essentially due to pulmonary hypertension and are not related to the site of the shunt. Symptoms and signs may develop at any age, but their appearance in older patients is more common with late reversal of the shunt in A.S.D. Cyanosis may be present from birth or develop at any time later in all three, but late reversal is most common in A.S.D. Women preponderate among patients with reversed shunts in A.S.D. but the sexes are about equally affected in V.S.D. and P.D.A.

Physical signs are dominated by those of pulmonary hypertension and reversal of the shunt. Differential cyanosis clearly points to a P.D.A. An early diastolic murmur that can be firmly attributed to aortic rather than pulmonary regurgitation points strongly to V.S.D. with involvement of an aortic valve cusp. Atrial fibrillation is more common with reversed shunts in A.S.D.

X-rays may be helpful but here also the main abnormalities are due to pulmonary hypertension. Evidence of anomalous pulmonary veins points to an A.S.D. A patent ductus may be suggested by local calcification in its wall or in the contiguous pulmonary artery, or by a bulge into the adjacent left bronchus. Differential size of heart chambers is helpful if left atrial or left ventricular enlargement is recognizable but it is usually not so in patients with great pulmonary hypertension. The electrocardiogram of each of these conditions tends to be similar when pulmonary hypertension induces shunt reversal, but sometimes a large R and deep S in mid-chest leads point to a V.S.D.

Passage of a cardiac catheter provides good evidence of the shunt site but a second shunt may be missed, a foramen ovale may cause error, and oxygenated blood from pulmonary regurgitation may suggest a V.S.D. when none exists. Catheterization of anomalous pulmonary veins indicates an A.S.D. Dye dilution curves should indicate early or late passage across to the left side; systemic vasodilators should cause a fall in pulmonary arterial pressure in reversed V.S.D. or P.D.A.; and a Valsalva manœuvre causes intensification of the shunt at A.S.D. level. All of these elaborate tests require further investigation to assess their accuracy in differential diagnosis.

W. Somerville. Retrograde arterial catheterization and angiocardiography would pick out the cases with a patent ductus. The condition might be reversible in the first year of life and an attempt should be made to establish the diagnosis at that age.

C. G. Parsons. Dr. Astley obtains satisfactory retrograde aortograms in children up to the age of 10 years by injecting into the brachial artery through a canula. This will demonstrate an open duct when there is left-to-right shunt or when pressures are balanced. Reversed flow is more readily diagnosed by venous angiocardiography.

R. M. Marquis. We have obtained good angiocardiograms using only a canula in the radial artery. When there is shunt reversal from birth, the aorta is characteristically small in persistent ductus, so a small aorta cannot be used as reliable evidence of an A.S.D.

L. McDonald. T1824 injections could be most helpful if the curves were acceptable.

M. B. McIlroy. The pattern of change recorded with an ear oximeter in response to Valsalva's manœuvre changed with the level of shunt.

R. E. Bonham-Carter. At Great Ormond Street we tend to establish the diagnosis by exploratory thoracotomy.

Brigden, Whittaker, and Campbell were critical about the term Eisenmenger's syndrome, but *Gibson, Somerville,* and *Wood* said it was convenient, because this was how the patient presented at the bedside.

(3) The Level of Pulmonary Vascular Resistance that Contraindicates Operation

Opened by W. P. Cleland

My own experience with the condition under discussion is limited, but it is of the greatest concern to us all now that surgery of ventricular septal defects (V.S.D.) is being undertaken in this country. The group of V.S.D. with hypertension is most important but we can use our experience of patients with P.D.A. and A.S.D. and hypertension to guide us in our approach. I shall not speak about the pathology of the pulmonary vessels nor about the mechanism of production of the hypertension, both of which have been discussed already.

I would like, first, to consider *patent ductus arteriosus* (P.D.A.) and to show a chart of a girl, aged 16, on whom I recently closed a ductus. The pulmonary artery pressure was 159/100, the aortic pressure 130/90; the systemic blood flow was calculated as 4 l./min., and the pulmonary flow as 6·3 l./min., making the pulmonary vascular resistance 17 units. I show this slide (Fig. 5) of the

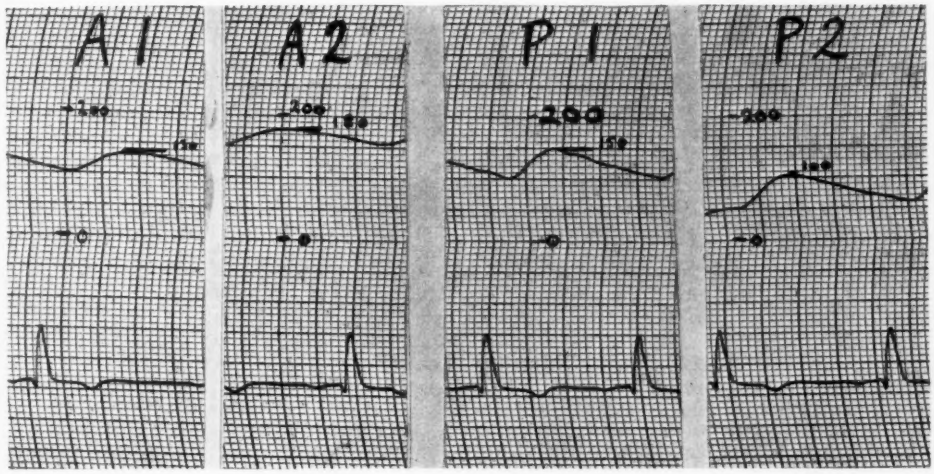


FIG. 5.—Tracings of pressure in the aorta and pulmonary artery before and after ligation of the ductus, (A) in the aorta and (P) in the pulmonary artery. (1) Before operation, and (2) after operation.

aortic and pulmonary arterial pressures before and after occlusion of the duct, not because it is unusual, but because it is what we expect in this group of cases.

Altogether I have treated 14 patients, 4 adults and 10 young children, with hypertension and a ductus, all still shunting from left to right. One had an associated A.S.D. and another a V.S.D. The post-operative course was uneventful in all but two: one who had a stormy period with cardiac failure was the child with the V.S.D. My experience suggests that even with balanced pressures there is usually an immediate fall in the pulmonary arterial pressure and a simultaneous rise in the aortic pressure, and that the prospects of a satisfactory outcome of a surgical closure are extremely good. Silver *et al.* (1954) from the Mayo Clinic have demonstrated a marked reduction in pulmonary pressures and a fall in pulmonary vascular resistance by late post-operative catheterization.

The situation is different with *atrial septal defects*. There are more middle-aged patients presenting with hypertension, and this complication appears to be more dangerous from the surgical point of view. The pathological changes in the pulmonary arteries and arterioles are degenerative in type with narrowing of the lumen from intimal fibrosis and proliferation. Campbell *et al.* (1957), Bedford *et al.* (1957), and Edwards *et al.* (1955) have all described these changes occurring in their series and almost every reported surgical series describes one or two patients dying from this complication. The sudden reduction in pulmonary blood flow following closure of the defect seems to precipitate a thrombotic obstruction which may result in death. I have had one patient developing a pulmonary infarct on the second day after operation, presumably from complications of this sort, although fortunately the patient survived.

Turning to the *ventricular septal defects* I am obliged to rely mainly on reported cases—the extensive series from Minneapolis (Warden *et al.*, 1957) and from the Mayo Clinic (DuShane *et al.*, 1956). The former group point out that most of their patients had pulmonary hypertension and

that the average pulmonary pressure was 70 per cent of the systemic and think that the risks of operation are increased in the presence of hypertension. The Mayo Clinic have presented a very well-documented account of the first 20 they have closed with the aid of the Gibbon machine. Eleven of their patients had a pulmonary arterial pressure of 80 per cent or more of the systemic pressure. In nine the pulmonary vascular resistance lay between 7·5 and 17 units, while in seven it was between 3 and 7 units. All patients, however, had a left-to-right shunt, the average shunt being 54 per cent, though in six there was a small right-to-left shunt also. Pressure recordings taken immediately before and after closure indicated an immediate fall in pulmonary pressure and their behaviour, in very many ways, was similar to that of the patients with a ductus and hypertension. There were 4 deaths in their first 20 cases, all due to pulmonary complications (atelectasis, bronchitis, etc.).

This work suggests that the V.S.D. is in many respects similar to the P.D.A. but behaves differently from the A.S.D. My present view is that I will be prepared to attempt the closure of a V.S.D., even when pressures are balanced and the resistance is high, provided there is still a reasonable left-to-right shunt, but this view is based on the experience of others and not my own.

M. Campbell. I am surprised that a girl with a pulmonary vascular resistance of 17 units has done well, for generally a level much lower than this contraindicates operation. In patients with ventricular septal defect the resistance tends to rise with age and so perhaps we should aim at operating on younger patients.

P. Wood. There must, I think, be a mistake in the calculation of the resistance or the patient may have been hypertensive with a raised systemic resistance.

A. Leatham. Findings at catheterization do not always reflect the patient's normal state, and the electrocardiogram may be a more reliable guide than a single reading of pulmonary pressure.

R. M. Marquis. Unfortunately persistence of a left-to-right shunt at catheterization does not necessarily imply that operation will be successful. Of six patients with a raised pulmonary vascular resistance and small left-to-right shunts through a persistent ductus but without shunt reversal, three died suddenly after operation, two within 24 hours and the third five months later with increasing dyspnœa and angina. The three remaining patients aged 8, 10, and 23, were recatheterized one to four years after operation and the pulmonary vascular resistance remained raised, though the pulmonary systolic pressures were lower but still in the region of 60–70 mm. Hg.

W. Somerville. A patient who had an A.S.D. and a pulmonary vascular resistance of 8 units died at operation. I do not as a rule recommend operation for A.S.D. if the resistance exceeds 5 units.

R. Gibson. One patient with A.S.D. and a raised resistance had thrombosed the whole of her pulmonary vascular bed during the period of circulatory arrest at operation.

J. D. Hay. A shunt that is usually from left-to-right may become balanced or reversed during operation owing to the fall in systemic pressure during anæsthesia. The only death in the first 100 children operated upon by Mr. Edwards was in such a child: because the shunt at operation was from right-to-left he did not close the ductus and the child died shortly after the operation: had he closed it, she might have lived.

W. P. Cleland (in reply). Surgery cannot, I think, help patients with right-to-left shunts. There is a serious risk of thrombosis during circulatory arrest for operation on an A.S.D. with raised pulmonary vascular resistance.

Differential Diagnosis of Fallot's Tetralogy and Simple Pulmonary Stenosis with a Reversed Inter-Atrial Shunt

Opened by Maurice Campbell

I propose to give you 18 points that help to distinguish Fallot's tetralogy from simple pulmonary stenosis. The first five are more likely to be found in Fallot's tetralogy, where the physique is generally poor and the chest often deformed (1); where squatting occurs in 85 instead of 15 per cent (2); where the clubbing of the fingers is more severe (3); where the cyanosis occurs earlier,

nearly always before eighteen months (4); and where it is generally more severe, the hæmoglobin ranging between 120 and 149 with an average of 134 per cent (5), while in simple stenosis it ranges between 100 and 139 and averages 120 per cent. In contrast there may be a greater increase of cyanosis on exertion in simple pulmonary stenosis.

The next four points are physical signs. These are less striking in Fallot's tetralogy, where their value is negative rather than positive. On the other hand, in simple pulmonary stenosis of any severity, and cyanotic cases must be severe, there is a prominent *a* wave in the jugular pulse (6), the systolic murmur is louder and longer (7), the degree of splitting of the second sound is increased during expiration by delay in pulmonary valve closure (8), and the aortic component is not increased (9) as it may be in Fallot's tetralogy.

The next five points deal with radiology and the electrocardiogram. In Fallot's tetralogy the heart is of normal size unless there are complications (10), there is a deep pulmonary bay (11), and strikingly oligæmic lung fields (12). In cyanotic pulmonary stenosis the heart is nearly always enlarged and may be greatly so (10), the pulmonary artery is more dilated beyond the stenosis and tends to fill in the pulmonary bay (11), and the lung fields are less oligæmic (12) for until a late stage the pulmonary flow is kept at a normal level by the hard work of the right ventricle. The aortic arch is right-sided in 25 per cent of cases of Fallot's tetralogy and rarely in pulmonary stenosis (13). In both the cardiogram shows right ventricular preponderance but severe right ventricular strain with T inversion to V4 favours simple pulmonary stenosis (14).

Catheterization may be decisive for in Fallot's tetralogy the right ventricular pressure is about the same as the systemic, while in simple pulmonary stenosis it differs from the systemic in three-quarters (15), ranging between 40 and 200 mm. Evidence that the stenosis is infundibular makes Fallot's tetralogy more likely (16) but does not, of course, exclude a closed ventricular septum.

Angiocardiography should show the shunt from the right to the left atrium (17), and there is less likely to be simultaneous filling of the pulmonary trunk and aorta (18).

With all these differences it may seem that there should never be much difficulty, but most of them are usual rather than universal and there is overlapping. Difficulty is most likely to arise in patients with Fallot's tetralogy who are relatively fit with little cyanosis or sometimes in those with extreme ventricular strain. When there is difficulty, angiocardiography should give the most decisive answer, but the differential diagnosis has been expressed in this way because the general picture, taking all these differences into account, is more likely to give the right answer than any one alone. Whether studies with dye curves will give a more decisive answer is still uncertain.

J. D. Hay. In infancy some of the differentiating points mentioned by Campbell will let one down: for example, in pulmonary stenosis with an A.S.D. cyanosis may be extreme and the pulmonary arc on X-ray may be concave because there has not been time for post-stenotic dilatation of the pulmonary artery to develop. Angiocardiography is the most reliable method of differentiating these lesions in infancy: occasionally the hypertrophy of the right ventricular wall so encroaches upon its cavity that it is not visualized by dye, which, with the filling of the left atrium from the right suggests tricupid atresia: right ventricular dominance in the cardiogram should prevent this misinterpretation.

R. E. Bonham-Carter. An infant with Fallot's tetralogy who becomes anæmic or relatively anæmic can have a very large heart (reversible on correction of the anæmia) and this can make one think first of pulmonary stenosis with reversed inter-atrial shunt.

J. Shillingford. Studies with T1824 have proved of value at the Mayo Clinic.

M. B. McIlroy. We have been deceived by dye curves in this situation: maximum information should be sought in every way.

R. Gibson. In two cases, both with large *a* waves, the right ventricular systolic pressure was 50 and 100 mm. Hg greater than the systemic, but both had Fallot's tetralogy at operation.

P. Wood. One can be deceived by artefacts on right ventricular tracings which should always be scrutinized carefully.

M. Campbell (in reply). All the evidence must be weighed in each case. The differentiation cannot be made on a single test, though perhaps angiocardiography is the most decisive.

The Selection of Cases of Simple Pulmonary Stenosis for Surgical Treatment

Opened by David Waterston

Many surgeons have become dissatisfied with the "blind" right ventricular approach to the outflow tract, and now prefer to deal with the stenosis under direct vision through the pulmonary artery or the right ventricle. The slightly greater risk with this procedure makes the indications for surgery difficult at the present time.

There is no doubt that surgery should be advised in any case showing one or more of the following features.

(1) *Cyanosis*, whether this be due to a right-to-left shunt through an unsealed foramen ovale or not.

(2) *Clinical signs of right ventricular strain*, such as diminution in exercise tolerance, angina, or enlargement of the heart. Electrocardiographic evidence of right ventricular strain should not be relied on in young children.

(3) *A right ventricular pressure approaching the systemic level.* In the future it seems likely that all cases with a significant rise in right ventricular pressure should be subjected to operation; this should not be advised until the operative mortality approaches that for patent ductus, i.e. 1–2 per cent.

The operation of choice should allow for a direct vision approach with plenty of time to deal with the infundibular stenosis if necessary. Until this procedure becomes a safe one, the indications for operation must remain limited.

R. E. Bonham-Carter. Some children with pulmonary stenosis are cyanosed at rest, and standing makes them go nearly black. In two cases where I thought there was a right-to-left shunt, the septa were intact at necropsy. I therefore regard cyanosis—presumably peripheral—as an indication for operation. Cerebral disturbance is another indication: in two of three children, who had fits and abnormal electro-encephalograms, these returned to normal and the fits stopped after valvotomy.

J. D. Hay. It may be too late to wait for symptoms before advising operation: in 17 of 30 children symptoms were absent. We catheterize all our suspected cases in children and advise operation when the R.V. pressure is over 70 mm. In five with a pressure above this the cardiogram was normal.

W. P. Cleland. Anyone operating on pulmonary valve stenosis must have been dismayed by finding subvalvular obstruction at a later date, even though the valve had been well split. The present tendency is to open up the infundibulum and remove some of the muscle there though we have no clear idea as to how much should be taken away. Is there any need to do this?

P. Wood. I believe there is; if this functional stenosis is left, patients do badly, for the stenosis and the muscular hypertrophy do not subside. Surgical removal of infundibular muscle does not give a good result and valvular stenosis is best operated upon before this functional stenosis appears. At present I recommend operation in patients with R.V. systolic pressures of 75–80 mm. Hg. Now that valvotomy under direct vision is giving better results perhaps milder cases with pressures of 50–60 mm. should be sent for surgery.

H. E. Griswold (of Oregon, U.S.A.). The transventricular approach should not be abandoned too readily. With it, and using a special knife, my surgical colleagues are usually successful in reducing the valvular gradient to 10 or 20 mm. Hg.

W. P. Cleland. Is the development of functional infundibular stenosis a question of time or is it related to the degree of valvular obstruction?

P. Wood. It never occurs with mild stenosis. It can occur with moderate stenosis and this may be devastating. I do not know when it begins but in severe stenosis it can be fully developed when the child is 8 years old.

C. G. Parsons. Cine-angiocardiograms taken by Dr. Astley in a child with valvular stenosis showed a wide infundibular canal during ventricular systole. When the heart was examined at necropsy a false impression of infundibular stenosis was produced by the tremendous muscular hypertrophy of the infundibular canal.

High R.V. pressure may make it impossible to demonstrate a septal defect by catheter. After successful operation for pulmonary stenosis and closure of an A.S.D., a child developed a large left-to-right shunt (double the systemic blood flow) through a previously unrecognized V.S.D.

D. J. Waterston (in reply). In our present state of knowledge the surgeon must always be prepared to open up the outflow tract when operating on pulmonary valve stenosis.

FOURTH SESSION — *CHAIRMAN: GRAHAM HAYWARD*

The Surgical Treatment of Pulmonary Stenosis complicated by A.S.D. with Direct or Reversed Shunt

Opened by J. D. Hay

Our experience in Liverpool is mainly confined to infants and children, and to a short follow-up, but this has raised some of the main questions. A decision about the advisability and type of surgical treatment for this combination of lesions has to be faced not infrequently now that both operations are reasonably safe. The presence of both lesions must, of course, be demonstrated, and the direction of the interatrial shunt established.

We have already discussed the significance of the pressure gradients across the pulmonary valve in the presence of a left-to-right shunt through an A.S.D. and it seems that we have to be very cautious in their interpretation. The site of stenosis must also be defined. Catheterization and selective angiocardiography is the best method of settling the site in all but infants and perhaps toddlers; in them a venous angiocardiogram is usually adequate and will, of course, reveal also a right-to-left shunt through an A.S.D. and help to differentiate the condition from Fallot's tetralogy.

With regard to the diagnosis of the A.S.D., firstly is an rsR′ pattern usually present when the shunt is from left to right and usually replaced by the pattern of R.V. strain when the stenosis is dominant and the shunt balanced or reversed? Or, to put it another way, when the stenosis is dominant is the absence of a rsR′ pattern against the presence of an A.S.D.? Not always, I think.

Secondly, when catheterization in a case of pulmonary stenosis shows no left-to-right shunt or one apparently at ventricular level, what other measures are of most value to demonstrate or exclude an A.S.D.? Should we always catheterize a case of pulmonary stenosis via the saphenous vein because an A.S.D. may be traversed much more easily by this route, even though it is more difficult to enter the pulmonary artery? Should we use a balloon catheter to estimate the size of the defect? I think it may be of value when the shunt is balanced or reversed, but may give a fallacious impression that the defect is small when in fact it is large, because it tends to catch on the wall of the defect on withdrawal. Or should we rather resort to angiocardiography, which will nearly always reveal the A.S.D. when there is a balanced or reversed shunt, but may not give much idea of its size?

As regards the indications of surgery, may I put forward our present view in Liverpool to stimulate discussion? If there is valvular stenosis and the right ventricular systolic pressure is over 45 mm. Hg and X-ray shows an absence of much pulmonary plethora, our aim is to avoid the continued strain of the combined lesions upon the right ventricle. Therefore, whether cardiac catheterization reveals a small left-to-right shunt through the defect or not, we would advise, and have in two cases advised, an immediate valvotomy, to be followed at once by closure of the defect if the condition of the patient permits. If no A.S.D. is found but only a small patent foramen ovale which might close spontaneously later, it might reasonably be left alone.

If a valvular stenosis is accompanied by a right-to-left shunt through the defect, as indicated by cyanosis, and if this is increasing or accompanied by dyspnœa, valvotomy is clearly the first step to

be undertaken when a complete correction is considered practicable. Following the valvotomy, a large A.S.D. should probably be closed at once, if possible, and a small one left alone in the hope that it may close spontaneously. In infants, valvotomy may be life-saving, as we have seen in one case. In some infants, an anastomosis may be more practicable and may be performed as a first aid measure with a view to valvotomy and closure of the A.S.D. later by open heart surgery.

If a left-to-right shunt through the A.S.D. is dominant, and there is much pulmonary plethora, the defect should be closed and the residual pressure gradient across the pulmonary valve, measured: if there is a significant valvular stenosis, valvotomy should follow, but we have had no such case.

P. Wood. The problem of what to do with an A.S.D. in patients with pulmonary stenosis arises because of the success of pulmonary valvotomy done under direct vision. The R.V. pressure may be reduced to a level where a large left-to-right shunt will appear. Is there any way of telling the size of the A.S.D. apart from estimates based on catheterization or angiocardiography?

M. B. McIlroy. Using the Valsalva manœuvre we can demonstrate the presence of a defect at atrial level but not its size. However, a patent foramen ovale appears to be too small to detect by this means.

D. J. Waterston. The problem will be solved when, with hypothermia, the surgeon feels for a defect as a routine.

P. Wood. This is not my experience and surgeons are already missing such defects: a cardiologist should be able to tell the surgeon beforehand whether a defect is present or not.

M. Campbell. I disagree with one of Hay's criteria for operation: a ventricular pressure of 45 mm. is just high enough to cut down an atrial shunt and the patient can safely wait until the surgeon is ready to deal with the pulmonary stenosis and the septal defect at one operation.

J. D. Hay (in reply). I should have made it clear that we are prepared to perform valvotomy and close the A.S.D. at the same operation if the condition of the patient permits. I agree with Wood that we physicians ought to make certain of the presence of an A.S.D. complicating pulmonary stenosis. Catheterization via the saphenous vein seems the most reliable method of achieving this with, perhaps, the employment of a balloon catheter, although I personally do not like using one because of the hazards mentioned.

Attacks of Deeper Cyanosis and Loss of Consciousness (Syncope) in Fallot's Tetralogy

Opened by Paul Wood

A history of syncope is obtained in about 20 per cent of all cases of Fallot's tetralogy, and is as common when the stenosis is valvular as when it is infundibular. Attacks are spontaneous and begin with increasing dyspnœa and cyanosis until consciousness is lost. Although the great majority recover, fatal syncope remains an important cause of death in Fallot's tetralogy, so much so that any patient giving this history receives high priority for surgical treatment.

It has been thought that the attacks are precipitated by a simple fall in blood pressure, such as occurs in vasomotor syncope in young persons; in Fallot's tetralogy a vasomotor turn of this sort immediately causes a sharp increase in the right-to-left shunt as the peripheral resistance decreases. This situation can be reproduced easily enough by giving a vasodilator substance such as amyl nitrite. Fig. 6 and 7 show the effect. There is an immediate fall in blood pressure accompanied by cyanosis and a drop in the arterial oxygen saturations; simultaneously the pulmonary artery pressure pulse declines both in the mean level of pressure and in the amplitude of the pulse.

Five cases of Fallot's tetralogy with a history of syncope have been studied. The findings have been uniform whether in an actual attack of syncope or in an episode of spontaneous dyspnœa and cyanosis short of syncope. Table I summarizes the findings and from them the following comment can be made.

(i) The blood pressure did not fall in any of the attacks. A peripheral vasoconstrictor (methedrine) was given in one case, and although the blood pressure rose from 100 to 150 mm., the extremely low arterial oxygen saturation (below 10%) remained unchanged. It is concluded with confidence that peripheral vasodilatation is not the cause of these attacks.

(ii) A consistent finding was the shortening, softening, and eventual disappearance of the pulmonary systolic murmur according to the degree of fall in arterial oxygen saturation. When consciousness was lost no murmur could be heard at all, suggesting that there was then a state of functional pulmonary "atresia". The extremely low arterial oxygen saturation confirmed that this was the actual cause of the loss of consciousness, and it is obvious that during the attack there is a largely increased deviation of blood from the lung, i.e. a sharp increase of right-to-left shunt.

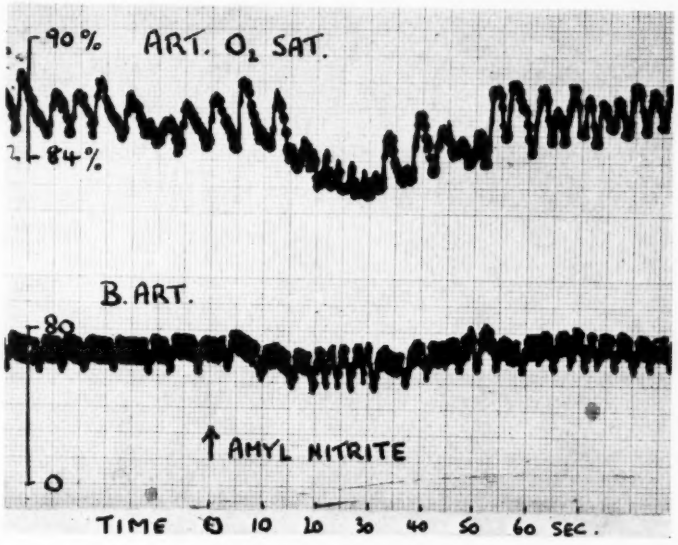


FIG. 6.—Effect of amyl nitrite on the brachial artery pressure and arterial oxygen saturation in Fallot's tetralogy.

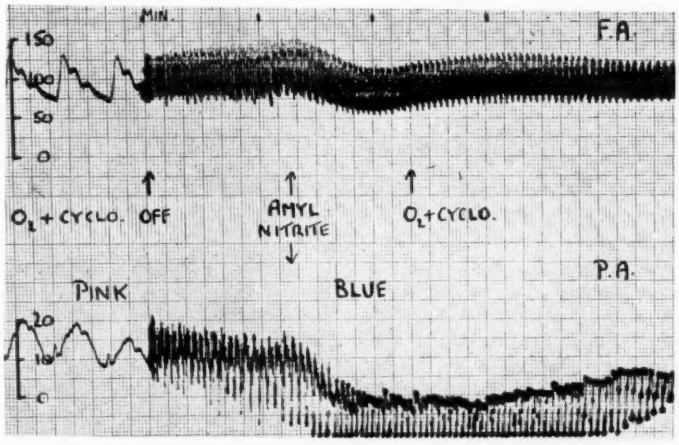


FIG. 7.—Effect of amyl nitrite on the pulmonary artery pressure and pulse (lower curve) and femoral artery pressure (upper curve) in Fallot's tetralogy. The sharp negative pressure swings in the P.A. tracing represent inspiration.

TABLE I

CHANGES DURING ATTACKS OF CYANOSIS AND DURING SYNCOPE IN FALLOT'S TETRALOGY

	Usual state	In attack of dyspnœa and cyanosis	During syncope
Cyanosis	Slight	Moderate	Severe
Arterial O_2 saturation	Around 80%	Around 50%	Around 20%
Pulse rate	Approx. 90	Approx. 120	Approx. 150
Jugular venous pulse	Normal	Normal	Normal
Pulmonary ejection murmur	Loud and fairly long	Soft and short	Absent
Thrill	Present	Absent	Absent
P.A. pressure	Fair	Low	Very low
P.A. pulse..	Good	Poor	Absent
B.P. (systemic)	Normal	Unchanged	Unchanged

(iii) When discussing this problem with Howard Burchell in 1953, he suggested that the cause might well be breath-holding, a not uncommon phenomenon in infants and small children when emotionally disturbed. This might well cause pulmonary vasoconstriction secondary to a fall in alveolar oxygen tension. If this was the explanation, however, the pulmonary arterial pressure would rise. But on several occasions when increased cyanosis occurred during catheterization, the opposite was always found, as indicated in the Table. It follows that the deflection of blood from the lungs cannot be due to pulmonary vasoconstriction.

(iv) There is only one other anatomical site that might vary its resistance and so influence the quantity of blood sent to the lungs and the amount of the shunt, namely the infundibulum of the right ventricle. Since functional infundibular stenosis is common when the congenital stricture is at valve level, varying behaviour of the infundibulum would be expected to operate particularly in cases of Fallot's tetralogy with valve stenosis; or at any rate it would be expected to affect such cases at least as frequently as those with organic infundibular stenosis, and this has already been shown to be true. The thesis suggested is that during the attacks the infundibulum contracts more completely than usual and tends to block the outflow to the lungs. This would cause the murmur to shorten, and to disappear when the obstruction was complete. This, too, has been shown to occur.

In two cases observations made during catheterizations support this view. One patient, for example, was being anæsthetized with cyclopropane and was also having oxygen. It was noticed that the child was pink and that the pulmonary arterial pressure pulse was of high amplitude and running at a good mean pressure (Fig. 8). When both oxygen and cyclopropane were withheld the child became cyanosed. During this phase the murmur shortened and the pulmonary arterial pressure pulse declined sharply, both in mean pressure and amplitude. When oxygen was given the patient's colour improved somewhat, but he remained cyanosed, the murmur did not increase in length or intensity, and the arterial pressure pulse did not regain its proper contour or pressure level. When cyclopropane was added, however, there was a rapid change in the situation; the child turned bright pink, the murmur lengthened and became loud, and the pulmonary arterial pressure pulse regained its normal pressure and amplitude of pulsation. These events are summarized in Fig. 9. It is concluded that cyclopropane relieved infundibular over-action.

No information is available concerning the precise cause of the variability in infundibular behaviour, nor whether the effect of cyclopropane is specific or whether many other anæsthetics or strong sedatives would have the same effect. Taussig's original observation that the best treatment

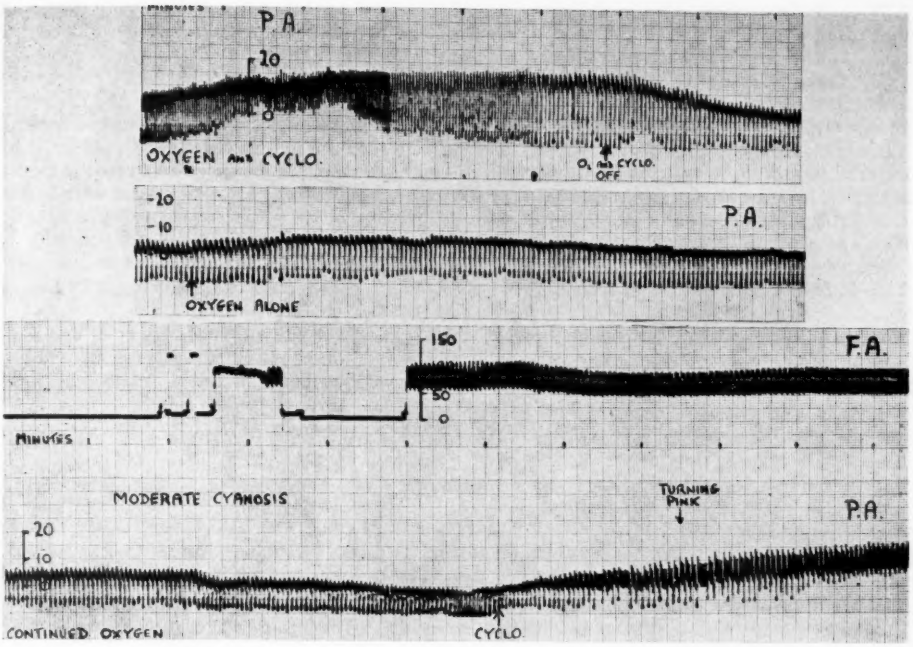


FIG. 8.—Continuous tracings, showing the effect of oxygen and cyclopropane on the pulmonary artery pressure pulse and skin colour in Fallot's tetralogy.

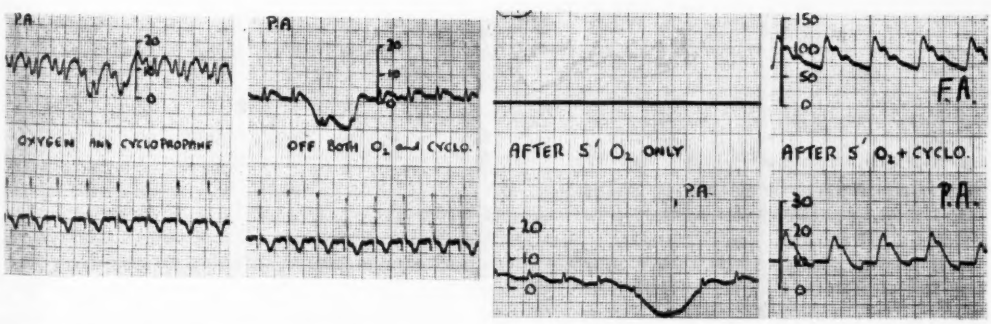


FIG. 9.—Selected tracings, showing the effect of oxygen and cyclopropane on the pulmonary artery pressure pulse in a case of Fallot's tetralogy. P.A., pulmonary artery; F.A. femoral artery.

of these attacks is morphine suggests that the action of cyclopropane may be non-specific. The thesis, however, is not so much that cyclopropane may relieve syncope in Fallot's tetralogy, but that the cause of the syncope is due to functional obstruction in the infundibulum and not to systemic vasodilatation nor to pulmonary vasoconstriction, although it is conceded that under special circumstances such mechanisms might be responsible.

W. Somerville. What initiates this functional infundibular stenosis and is it ever provoked by catheterization or angiocardiography?

P. Wood. The attacks appear generally to be spontaneous though sometimes initiated psychologically. A point against the theory put forward is that one of my patients with pulmonary atresia had syncopal attacks.

B. G. B. Lucas. I have often noticed that when patients with Fallot's tetralogy are anæsthetized they became less cyanosed. Probably there is nothing specific in the action of cyclopropane and the treatment of syncope might be to render the patient quickly unconscious, for example with intravenous morphine.

J. D. Hay. In support of this observation is the fact that when children are anæsthetized, as for an angiocardiogram, they become less cyanosed. Wood's observations may partly explain why angiocardiography under general anæsthesia may suggest a wide infundibular canal in cases in which considerable infundibular stenosis is found at operation or autopsy.

W. Somerville. In hospital syncope is treated with oxygen and the patients recover (or, said *Wood*, they die).

B. G. B. Lucas. A patient with bronchospasm rarely dies for when he becomes unconscious and anoxic there is muscular relaxation.

P. Wood (in reply). There is probably nothing very specific about the action of cyclopropane. Aminophyllin has failed to relieve the attacks. The syncopal attack produces unconsciousness more quickly than does cyclopropane and it might therefore be argued that oxygen was contraindicated.

The Differential Diagnosis of Shunts by Respiratory Techniques

Opened by M. B. McIlroy

When a patient with a small or moderate shunt through an A.S.D. performs Valsalva's manœuvre, the arterial pressure falls off in the normal manner as the heart and lungs empty of blood. When the patient stops blowing, the venous return is restored and blood rushes into an empty right atrium: this produces a momentary increase in right atrial pressure which reverses the shunt and leads to a temporary fall in arterial oxygen saturation of 2–5 per cent, about three seconds after the pressure is released because of the heart-to-ear circulation time: this can be recorded using an ear oximeter. This sequence of events was described by Lee and Gimlette (1957). In patients with a large shunt at atrial level the response is different because the patient has a square wave Valsalva response and no shunt reversal occurs when the patient stops blowing. This test has been performed in 50 patients with an A.S.D. and those with pulmonary to systemic flow ratios of 4:1 and over tend to have square wave Valsalva responses while those under 4:1 tend to have a normal response and show shunt reversal either at rest or after exercise. These results confirm the work of Lee and Gimlette (1957) and show that this is a useful simple test for the detection of A.S.D. The test is not positive when there is a patent foramen ovale. It is useful in deciding if the defect has been completely closed at operation and should pick out cases with anomalous venous drainage of the right lung with an intact atrial septum.

The test is also useful in other forms of congenital heart disease, but uncomplicated shunts at ventricular or ductal level cannot be reversed. In patients with right-to-left or bidirectional shunts there are considerable changes in saturation during and after Valsalva's manœuvre which vary with the level of the shunt. Fig. 10A shows the pattern in reversed shunt at ventricular level in a patient with Fallot's tetralogy. The saturation first falls due to the inspiration before the blow, and then rises due to reduction in the right-to-left shunt; there is then a fall in saturation during the period of blowing which is the most distinctive feature of this response and is unexplained. The continued fall after Valsalva is due to resumption of the venous return.

The pattern found in reversed shunt at atrial level is different (Fig. 10B). Here the saturation rises throughout the period of blowing. The third pattern, found in patients with reversed shunt at aorto-pulmonary level, is shown in Fig. 10C. It resembles the pattern seen in interatrial shunt but the drop in saturation after Valsalva is delayed and prolonged, being maximal 7 seconds after the release of pressure. This is probably due to the increased pathway the blood has to travel through the right heart before reaching the shunt. The position is analogous to dye injection into the right atrium, except that the "dye" is venous blood. If the reversed shunt is at atrial level,

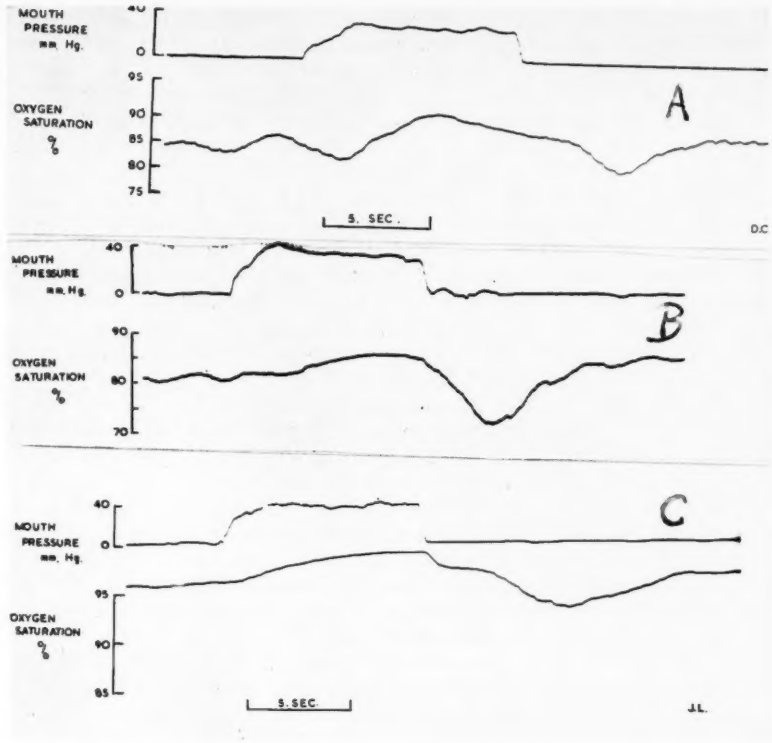


FIG. 10.—Arterial oxygen saturation during Valsalva's manœuvre in patients with a reversed shunt at (*a*) ventricular, (*b*) atrial, and (*c*) aorto-pulmonary level.

the appearance time is short and the fall in saturation is abrupt. If the reversed shunt is at ductus level, the appearance time is longer and the fall in saturation is more spread out.

This short account of the use of Valsalva's manœuvre to produce different patterns of saturation change in different types of congenital heart disease has, I hope, been sufficient to show that this simple test can be of value in the diagnosis of congenital heart disease.

A. Leatham. How many normal subjects have been studied? The manœuvre might produce shunt reversal through a patent ovale.

M. B. McIlroy. Ten normal subjects have failed to show shunt reversal as did two patients with pulmonary stenosis who were known to have a patent foramen ovale. It is unlikely that normal subjects could show detectable shunt reversal through a foramen ovale.

P. Wood. It is important to establish this beyond argument before using the test post-operatively to confirm that an A.S.D. had been completely closed.

DYE DILUTION CURVES IN CONGENITAL HEART DISEASE

OPENED BY J. P. SHILLINGFORD

Stewart first showed the possibility of measuring the cardiac output by injecting an indicator substance into the venous circulation and sampling it in the arterial circulation. Hamilton and his

associates confirmed these results in circulation models and demonstrated that an estimate of the volume through which the indicator had passed could be made by an analysis of the time concentration curve.

More recently Swan and his associates at the Mayo Clinic have made extensive use of the dye dilution technique for detecting the presence and position of intracardiac shunts. The technical problem of recording the concentration curves from either the ear or an arterial cuvette has in the past been considerable. With the development of suitable electronic amplifiers and recorders this has now been largely overcome and satisfactory curves can be recorded with little trouble. Evans blue (T1824) has been the indicator mainly used and its passage through the ear or a cuvette can be recorded by a photo-electric cell with a red filter; it has the disadvantage that its absorption spectrum falls within that of reduced hæmoglobin so that changes in oxygen saturation effect the curve. The introduction of a green dye (tricarbo-cyamine) may eliminate this trouble. Radioactive indicators have proved unsatisfactory for continuous sampling from a peripheral artery.

The dye dilution curve in the absence of a shunt is a "skew" distribution curve with an appearance time some seconds after the injection depending on the cardiac output and the volume that the dye passes. The upstroke is smooth in outline and the downstroke exponential in form. The introduction of a right-to-left shunt causes an earlier appearance time and a small hump on the upstroke of the curve, by some of the dye particles passing into the arterial circulation ahead of the main part of the dye which passes through the lungs. The introduction of a left-to-right shunt does not alter the appearance time, but produces a series of small curves on the descending limb of the main curve due to small portions of the dye being sequestered by the shunt and passed on from subsequent pulmonary circulations. This also increases the overall spread of the curve.

Although these changes may be used as a simple screening test to show the presence of a right-to-left or left-to-right shunt they become far more valuable in diagnosing the lesions of congenital heart disease when used in association with selective injection through a cardiac catheter.

Exact localization of left-to-right shunts is made by injecting the dye through a catheter into the chamber concerned with the shunt and comparing the curve with a second injection made more distally and separated from the chamber by a competent valve. For example in V.S.D. left ventricular injection causes an abnormal and aortic injection a normal curve. In a similar way the localization of an A.S.D. may be made and the position of an aorto-pulmonary shunt in the region of the sinus of Valsava localized and separated from a P.D.A.

It is often difficult in cases of A.S.D. where the catheter has entered the pulmonary vein to know whether the vein enters the right or left atrium. The introduction of dye down the catheter and its recording as a dye dilution curve determines this by comparison with a curve drawn by injection into the superior vena cava in the same patient.

Differentiation between Fallot's tetralogy and pulmonary stenosis with reversed intra-atrial shunt can be made by injection into the right ventricle and right atrium. In the former case an abnormal curve is obtained only from the right ventricle and in the latter from the right atrium.

These examples illustrate some of the potentialities of the technique which is still in its infancy. It has, however, probably already reached the stage when it is ready to take its place alongside the cardiac catheter and angiocardiogram in the exact anatomical diagnosis of congenital heart lesions.

R. W. Emanuel. I have studied three patients where the diagnosis lay between Fallot's tetralogy and a reversed interatrial shunt. By injecting dye into the right ventricle the correct diagnosis was reached in each case. A further use is that if a patient has an A.S.D. an injection of dye into the inferior vena cava often passes across and produces an early appearance of the dye curve. This technique is of value when the catheter cannot be passed into the left atrium and where the rise in saturation at atrial level might be wrongly attributed to the presence of anomalous veins.

P. Wood. The technique is of value and facilities for dye injection should always be available during catheterization. It is particularly helpful in demonstrating the level of the shunt in patients with Eisenmenger's syndrome.

REFERENCES

Barber, J. M., Magidson, O., and Wood, P. (1950). *Brit. Heart J.*, **12**, 277.
Bedford, D. E., Sellors, T. H., Somerville, W., Belcher, J. R., and Besterman, E. M. M. (1957). *Lancet*, **1**, 1255.
Blount, S. G., Swan, H., Gensini, G., and McCord, M. C. (1954). *Circulation*, **9**, 801.
—, Balchum, O. J., and Gensini, G. (1956). *Circulation*, **13**, 499.
Brandenburg, R. O., and DuShane, J. W. (1956). *Proc. Mayo Clin.*, **31**, 509.
Brewer, A. (1953). *Proc. Mayo Clin.*, **28**, 480.
Campbell, M., Neill, C., and Suzman, S. (1957). *Brit. med. J.*, **1**, 1375.
—, and Missen, G. A. K. (1957). *Brit. Heart. J.*, **19**, 403.
—, and Brotmacher, L. (1958). *Brit. Heart J.*, **20**, July.
Dexter, L. (1956). *Brit. Heart J.*, **18**, 209.
DuShane, J. W., Kirklin, J. W., Patrick, R. T., Donald, D. E., Terry, H. R., Burchell, H. B., and Wood, E. H. (1956). *J. Amer. med. Ass.*, **160**, 950.
Edwards, F. R., Farquhar, H. G., Hay, J. D., and Rees, G. J. (1955). *Brit. med. J.*, **11**, 1463.
Hamer, N. A. J. (1958). *Brit. Heart J.*, **20**, 215.
Leatham, A., and Gray, I. (1956). *Brit. Heart J.*, **18**, 193.
Lee, G. de L., and Gimlette, T. M. D. (1957). *Brit. med. J.*, **1**, 1278.
Rokitansky, C. (1875). *Die Defecte der Scheidewande des Herzens.* Vienna.
Silver, A. W., Kirklin, J. W., Ellis, F. H., and Wood, E. H. (1954). *Proc. Mayo Clin.*, **29**, 293.
Swan, H. J. C., Burchell, H. B., and Wood, E. H. (1953). *Proc. Mayo Clin.*, **28**, 452.
—, Kirklin, J. W., and Wood, E. H. (1957). *Circulation*, **16**, 54.
Toscano-Barbosa, E., Brandenburg, R. O., and Burchell, H. B. (1956). *Proc. Mayo Clin.*, **31**, 513.
Warden, H. E., DeWall, R. A., Cohen, M., Varco, R. L., and Lillehei, C. W. (1957). *J. Thor. Surg.*, **33**, 21.

PROCEEDINGS OF THE BRITISH CARDIAC SOCIETY

An AUTUMN MEETING of the British Cardiac Society was held at the Royal Society of Medicine, Wimpole Street, London, on Friday, November 29, 1957. The Chairman, RAE GILCHRIST, took the Chair at 9.30 a.m.; 119 members and 22 visitors were present.

PRIVATE BUSINESS

1. The minutes of the last Annual General Meeting having been published in the Journal (**19**, 581, 1957) were taken as read and confirmed.
2. Maurice Campbell was re-elected President for a further period of one year, his two-year term of office expiring at the beginning of the next Annual General Meeting.
3. The Secretary reminded Members that communications submitted for the Third World Congress of Cardiology in Brussels, 1958, should be in his hands by February 1, 1958. Further details of the Belgian Society of Cardiology Prize could be had from him on application.
4. The Chairman announced that an invitation from Phillips to hold the Annual General Meeting in 1959 at Cardiff had been accepted.
5. The Chairman announced a decision of the Council, that as a general rule the Autumn Meeting of the Society would be held in London on the last Friday in October, in the alternate years when there was no meeting of the International or European Societies of Cardiology.

SCIENTIFIC COMMUNICATIONS

HÆMODYNAMIC STUDIES OF COARCTATION OF THE AORTA BEFORE AND AFTER OPERATION

By K. W. Donald, P. N. Wormald (*introduced*), J. M. Bishop, and S. H. Taylor (*introduced*)

This is a study of the systemic blood pressure, cardiac output, and pulmonary arterial and wedge pressures, at rest and on considerable exercise, before and after operation in coarctation of the aorta. Raised wedge pressures were found on exercise in a number of relatively young patients denying disability, and this is considered important evidence of incipient left ventricular insufficiency. These raised wedge pressures on exercise reverted to normal levels after operation in most cases. The increase in systemic blood pressure on exercise was still highly abnormal after operation even in very successful cases. Studies have also been carried out to estimate the leg blood flow in this disease during exercise, both before and after operation.

THE EFFECTS OF POSTURE ON PULMONARY DYNAMICS IN MITRAL DISEASE

By David Cardus (*introduced*), John Mackinnon, and Geoffrey Wade

Published in full: Brit. Heart J., **20**, 233, 1958

THE EVALUATION OF CHLOROTHIAZIDE, AN ORAL DIURETIC

By R. I. S. Bayliss, and David Marrack, J. R. Rees, and Joan Zilva (*introduced*)

Chlorothiazide has been investigated in metabolic and clinical studies. Its predominant action is to enhance the urinary excretion of sodium and chloride ions (similar to the effect of mercurial diuretics) but it also has a less significant action as a carbonic anhydrase inhibitor. Clinically it is as potent as intramuscular mersalyl, and is often effective in patients who have become refractory to mercurial diuretics.

EXCRETION OF MERCURY IN URINE DURING TREATMENT WITH MERCURIAL DIURETICS

By Frances Gardner and Cecil Symons (*introduced*)

The excretion of mercury in the urine following the parenteral administration of an organic mercurial diuretic, mercaptomerin, was studied in twelve patients. Two patients had no cardiac disease and ten had

congestive failure. Eight of these had no evidence of organic renal disease, though some of them had albuminuria on admission, which disappeared as failure cleared. The other two patients were in congestive failure, with heavy and persistent albuminuria of not less than 4 g. per litre per 24 hours; one of these two had malignant hypertension with renal damage and nitrogen retention.

All cardiac patients were adequately digitalized and were on a low sodium diet without restriction of fluids. Twenty-four-hour specimens of urine were collected before and after each subcutaneous injection of 2 ml. mercaptomerin, and analysed for mercury content using Varley's method of extraction. Urinary electrolytes were also estimated.

It was found that in congestive failure without organic renal disease, the volume of urine passed in the 24 hours after the injection of mercaptomerin was directly related to the mercury excreted during this time. A poor response on one occasion did not mean that the patient would continue to have an unsatisfactory response on subsequent occasions. In the two patients with severe and persistent albuminuria retention of mercury occurred, even though there was a diuretic response.

Nil Desperandum

By N. R. Barrett

I would like to report the clinical records of a middle-aged man who came to me originally suffering from a fibro-sarcoma of the mediastinum overlying the heart. The tumor was large and was removed surgically. It did not, at that time, invade the pericardium. Some years later the patient returned to me suffering from a large recurrent tumour invading the anterior chest wall on the left side. There was nothing to suggest that the heart was involved. I removed the recurrence together with a large segment of the chest wall, the anterior pericardium, and a piece of the front of the right ventricle (measuring approximately 5 by 2·5 cm.). The patient is alive and moderately fit eight months later. There is, as yet, no further recurrence.

The Measurement of the Prevalence of Coronary Heart Disease

By A. J. Thomas

A technique for comparing the prevalence of coronary heart disease in different areas is described. It involves the clinical, radiological, and electrocardiographic examination of a properly defined random sample of a population. Observer differences occur and so the cardiograms have been circulated to other observers for independent readings. The task of arranging multiple clinical examinations has been too great. The earlier observer differences in reading the electrocardiograms have been large, but it is hoped that the experience will lead to the better definition of the abnormal and the use of more precise form for recording the findings of the observer. The interpretations of the changes of ventricular hypertrophy and ischæmia have caused some of the differences.

Other facts have been recorded in the course of the survey, such as blood pressure levels, body measurements, family histories, and blood cholesterol levels. The subjects with coronary heart disease seem to be taller and heavier but not more obese, and have a slightly higher blood pressure. There has been a lack of association between blood cholesterol levels and the prevalence of coronary heart disease among men in the 55–64 age group.

The final corrected prevalence figure for men aged 55–64 years has been made on the electrocardiogram: it was 17·5 per cent in the rural community and 21·3 per cent in the mining community.

Further work is required on similar populations, with particular regard to the choice of controls and the interpretation of the electrocardiograms.

The Nature of the Arterial Narrowing in Pulmonary Hypertension

By D. S. Short

Post-mortem arteriography has demonstrated two distinct pathological processes affecting the arteries in the periphery of the lung in cases of pulmonary hypertension. One is obstruction within the vessels; the other is diffuse narrowing of the vessels.

The diffuse narrowing is organic in nature, and not a mere spastic or neurogenic vasoconstriction. Although the arterial wall appears hypertrophied, the narrowing of the lumen is not due to hypertrophy, but to a state of persistent contraction which has been termed arterial contracture. The apparent medial hypertrophy is due to the shortened circumference of the artery.

The Diagnosis of Mitral Regurgitation from Left Atrial Pressure Curves

By Bertrand Wells

Fifty pressure tracings were taken by direct puncture of the left atrium in mitral regurgitation. Left ventricular tracings were taken at the same time, and the degree of mitral regurgitation was estimated by the surgeon's finger in the left atrium. Copies of typical atrial and ventricular curves were superimposed in order to investigate the relationships more easily. As a control one hundred tracings were taken in a similar manner in patients before and after mitral valvotomy, when no mitral regurgitation was present.

The established criteria for the diagnosis of mitral regurgitation from pressure tracings have been examined. They appear applicable only to the more severe degrees of regurgitation, and are sometimes fulfilled when there is no mitral regurgitation.

New criteria have therefore been proposed by which it is possible to identify lesser degrees of mitral regurgitation from pressure tracings. These criteria require left ventricular as well as atrial curves, and depend on the rise of pressure in the atrium during the first third of ventricular systole. This must be taken from the point of separation of atrial and ventricular pressures in order to eliminate the synchronous pressure rise that occurs in some patients.

The Value of the Præcordial Acceleration Cardiogram in Differentiating Dominant Mitral Stenosis and Regurgitation

By Patrick Mounsey

The object of this investigation was to see whether præcordial pulsations reflect the differing mechanics of left ventricular filling in mitral stenosis and mitral regurgitation, and hence whether their recording might prove of value in the selection of patients for mitral valve surgery.

The præcordial pulsations of 32 patients with mitral valve disease were examined clinically and recorded in the præcordial acceleration cardiogram. Eight were judged to have pure regurgitation; and twelve dominant stenosis, proven at mitral valvotomy. Twelve had dominant regurgitation with stenosis also: of these seven had been rejected for mitral valvotomy, two developed dominant regurgitation after successful valvotomy, two were found to have dominant regurgitation with trivial stenosis at operation, and in one autopsy proof of the diagnosis was obtained.

The diastolic rapid inflow check, which corresponds to the third heart sound, was augmented in six of the eight patients with pure mitral regurgitation and in these the lesion was clinically most severe. The rapid inflow check was abnormally early in all 12 patients with dominant stenosis and often of small amplitude. Finally in the group with dominant regurgitation the rapid inflow check was more abrupt than in the other two groups and always large: its timing varied, being sometimes normally placed as in pure mitral regurgitation and sometimes premature as in dominant stenosis.

The præcordial acceleration cardiogram appears to reflect the dominant type of mitral valve lesion and hence may prove of value as an ancillary diagnostic aid in the selection of patients for mitral valve surgery.

The Calibration of Continuously Recorded Dye Dilution Curves

By R. W. Emanuel

A simplified method for the calibration of dye curves has been developed which is applicable to curves by cuvette oximetry or density. This involves collecting a sample of the blood which is being withdrawn while the dye curve is inscribed. Calibration is carried out by determining the mean concentration of dye in this sample and determining the mean deflection over the period of collection. Errors involved in calibrating from the "tail" of the dilution curve are therefore avoided. A syringe pump and special cross-over stopcock have been designed for this work.

The accuracy of the method has been tested *in vitro* and *in vivo*. *In vitro* when the output obtained by the method described was compared with a fixed output through a hydraulic system, the S.D. was $\pm$ 2·18 per cent and when compared with the Hamilton method in dogs the S.D. was $\pm$ 3·6 per cent. Clinical observations have comparable error. It is suggested that this method offers an accurate and simplified means of calibrating dye curves for clinical work.

Changes in the S–T Segment in Hypothermia

By D. Emslie-Smith (*introduced by Ian Hill*)

Published in full: Brit. Heart J., **20**, 175, 1958

The Effect of Exercise on the Electrocardiogram of Left Ventricular Hypertrophy

By John Wedgewood (*introduced by Graham Hayward*)

A study has been made of the effect of exercise on the electrocardiogram of left ventricular hypertrophy. The series consists of 100 patients with cardiographic signs of left ventricular hypertrophy due to hypertension, aortic valve disease, or patent ductus arteriosus.

Square depression of the S–T segment greater than 1 mm. developed in 21 per cent of the cases, in 61 per cent of those with angina and in 15 per cent of those without angina. 14 per cent developed reversal of previously inverted T waves. A further 12 per cent showed this change with square depression of the S–T segment, and 12 per cent developed inversion of previously upright T waves. The changes were correlated with the clinical, X-ray, and resting electrocardiographic findings.

The results suggest that the exercise test is a practical method of disclosing the presence of ischæmia even when the electrocardiogram shows the pattern of left ventricular strain. They also give some evidence of the incidence of coronary insufficiency in patients with hypertensive heart disease.

William Harvey and the Circulation of the Blood was shown at the end of the morning session. This film, based on the earlier one made by the late Sir Thomas Lewis and Sir Henry Dale for the Royal College of Physicians in 1928, has been remade in colour by the film unit of the Wellcome Foundation under the direction of Sir Henry Dale, F.R.S.

A film on the Jugular Venous Pulse produced by Paul Wood was shown at the afternoon session. It demonstrated clearly how much can be learned from a careful study of the jugular venous pulse. This film can be obtained from the Wellcome Foundation.

The Society dined together at the Savoy Hotel with the President in the Chair. Sir Henry Souttar attended as the Society's guest and spoke shortly about his first case of mitral valvotomy in 1925. The patient lived for several years and a photograph of the specimen was shown by William Evans.

ABSTRACTS OF CARDIOLOGY

Edited in collaboration with Abstracts of World Medicine

The Outlook for Children with Congenital Aortic Stenosis. I. B. BRAVERMAN and S. GIBSON. *Amer. Heart J.*, **53**, 487, 1957.

Since few detailed accounts have appeared of the course and prognosis of congenital aortic stenosis in children, the authors have reviewed 85 such cases in patients under 16 years (67 boys and 18 girls) seen during the past 8 years at the Children's Memorial Hospital, Chicago. None had a history of rheumatism, all had the classic physical signs of aortic stenosis, 2 had associated patent ductus arteriosus, 3 had aortic coarctation, and one had fibrocystic disease.

An examination has been made or a report obtained on 73 of these patients since January, 1956, their ages ranging from 3 months to 19 years. Of these, 41 have no symptoms, 26 have symptoms, and 6 (8%) are dead. Of the children who died, 4 did so very suddenly and 3 had at least one syncopal attack before the fatal one; in 4 the heart was enlarged and in 3 there were electrocardiographic signs of left heart strain.

Of the 67 survivors, 44 can compete with their contemporaries, 14 cannot do so fully, and 9 cannot compete at all. Of the 26 patients with symptoms, 9 are easily fatigued, 6 have headaches, 4 became dizzy, 4 are dyspnœic on exertion, 4 have epistaxis, and 3 have leg pains; in 5 of these children the heart is enlarged and in 10 there are cardiographic indications of left heart strain. Many of the 41 symptomless survivors are very active and several are athletes; 11 have large hearts and 14 have evidence of left heart strain.

The authors conclude that congenital aortic stenosis is not an innocent disease, and suggest that patients who are severely handicapped or have cardiac enlargement or electrocardiographic changes should be operated upon as soon as the procedure is proved to be relatively safe.

D. Emslie-Smith

Percutaneous Left Ventricular Puncture in the Assessment of Aortic Stenosis. P. FLEMING and R. GIBSON. *Thorax*, **12**, 37, 1957.

In order to determine the value of percutaneous left ventricular puncture in the preoperative assessment of aortic stenosis, 28 pressure records, have been analysed. All the patients concerned were considered to have aortic stenosis, and in 17 there was also clinical evidence of aortic regurgitation. The left ventricular pressure pulse in aortic stenosis is described. An "a" wave due to left atrial systole is usually present in the end-diastolic portion. The systolic pressure is high (ranging from 140 to 325 mm. Hg in the present series) and the pulse wave is more sharply peaked than normal, both isometric contraction time and ventricular systolic upstroke time being abbreviated. Owing to lengthening of the phase of reduced ejection, however, the total ventricular ejection period is prolonged.

Aortic valvotomy was subsequently performed on 18 patients, and a surgical estimate of the degree of stenosis was available for 16 of these. Neither the peak systolic pressure gradient across the valve nor the prolongation of the ventricular ejection period (corrected for differences in cycle length) proved to correlate closely with severity of stenosis, presumably because these parameters are appreciably influenced by variations in stroke volume and hence by the presence and degree of regurgitation. The calculated aortic valve area is not expected to agree precisely with the true area since in the presence of regurgitation measurement of output by the Fick principle underestimates the actual forward flow, while if stenosis is dominant the formula tends to overestimate valve size. Nevertheless, there was sufficient correlation to suggest that the calculated value may be of help in assessing doubtful cases. It is tentatively suggested that if it exceeds 1 sq. cm. and the degree of regurgitation is uncertain aortic stenosis is unlikely to be severe enough to warrant valvotomy.

Analysis of the brachial arterial pressure records confirmed the unreliability of the pulse pressure as an index of the degree of stenosis. The brachial systolic upstroke time, however, appears to be a more helpful measurement; this was invariably prolonged, and when related to the normal value for the pulse rate, correlated fairly well with the severity of the stenosis. *S. G. Owen*

Retrograde Perfusion of the Coronary Sinus for Direct Vision Aortic Surgery. V. L. GOTT, J. L. GONZALEZ, M. N. ZUHDI, R. L. VARCO, and C. W. LILLEHEI. *Surg. Gynec. Obstet.*, **104**, 319, 1957.

Retrograde perfusion, via the coronary sinus, of oxygenated blood, in combination with a pump-oxygenator, permits work on the open ascending aorta or coronary arteries for periods of up to 20 minutes in the dog. Flow studies of the coronary sinus venous drainage demonstrate in most instances a higher coronary flow in the bypassed heart even though the perfusion pressure in the aorta remains lower than for the non-by-passed heart. Twenty dogs were perfused seeking a survival experiment in each. Their hearts tolerated well 15 to 20 minutes of retrograde perfusion if the head of pressure was adjusted properly. The method of back perfusion via the coronary sinus has been tested in 7 clinical cases to date. In all instances the method appeared to protect the myocardium well against anoxia and coronary air embolism, permitting direct-vision reparative surgery for aortic stenosis and regurgitation, ruptured sinus of Valsalva, aortic-pulmonary septal defect, and complete transposition of the great vessels. The human heart responded well to this altered environment for periods up to 15 minutes.—[Authors' summary.]

Plasma Lipids and Proteins and Their Relationship to Coronary Disease among Navajo Indians. I. H. PAGE, L. A. LEWIS, and J. GILBERT. *Circulation (N.Y.)*, **13**, 675–679, 1956.

A review of the hospital records showed that myocardial infarction was diagnosed in only 5 full-blooded Navajo Indians among 10,276 admissions over 4 years to the Navajo Hospital, Arizona, and even in these 5 cases it was not confirmed by electrocardiography. Again, not one case of coronary arterial disease was observed among 60,405 out-patient attendances. In contrast, out of

20,289 white patients admitted to St. Joseph's Hospital, Albuquerque (about 150 miles distant), 146 had myocardial infarction; the age distribution was similar in the two groups. The Navajos are well nourished, and usually eat a typically American diet, often containing foods of high cholesterol and high fat content; they tend to consume less fruit and vegetables but more fried food.

The mean total plasma protein level among the Navajos was only slightly lower than that among a group of persons from Cleveland, Ohio; the albumin level was lower, while the globulin level tended to be slightly higher, especially the α- and γ-globulin fractions. The lipoprotein components were also very similar in the two populations. The mean total cholesterol value was about 50 mg. per 100 ml. lower in the Navajo group and did not alter with age. It is concluded that the lower serum cholesterol levels and the extremely low incidence of coronary arterial disease among the Navajo Indians cannot be attributed to a lower intake of fat, and that hereditary factors may be responsible.

Robert de Mowbray

Observations on the Morbid Anatomy of Coronary Artery Disease. A. W. BRANWOOD and G. L. MONTGOMERY. *Scot. med. J.*, **1**, 367, 1956.

An investigation of the pathological changes in the heart in 144 cases of sudden death and of clinically diagnosed coronary thrombosis is reported from the University of Edinburgh.

In all of the 26 cases of sudden death outside hospital a previous history of angina was obtained, and in none was an extracardiac cause of death found. Only 8 of these cases, however, showed coronary occlusion by recent thrombus or atheromatous softening; in 6 there was a non-occlusive thrombus and the rest showed no occluding material. There were 6 cases of recent infarction, only 3 of which had thrombi. In all cases there was gross atheromatous stenosis of all the coronary arteries and also evidence of myocardial fibrosis. In all 13 cases of sudden death in hospital (mainly postoperative) there was severe coronary stenosis and myocardial fibrosis; in this group were 3 recent infarcts without thrombosis and 3 cases of recent thrombosis.

Of the largest group examined, namely, 101 cases of clinical coronary thrombosis confirmed by electrocardiography, a recent infarct was found at necropsy in only 61, myocardial fibrosis alone in 25, minor muscle changes of dubious significance in 10, and no evidence of infarct or fibrosis in 5. Of the 61 cases of infarction, coronary occlusion was found in 24; in the rest non-occlusive thrombus was present in 23, no recent thrombus was detected in 13, and coronary embolism in one case. In most cases severe stenosis affected all three coronary arteries. Further, since only about 40 per cent of cases of infarction had a coronary occlusion the authors conclude that infarction is related to over-all coronary insufficiency rather than to occlusion of a particular artery.

Assessment of the age of the thrombi and infarcts by histological criteria showed that while most infarcts were at least several days old, the associated coronary thrombi appeared to be only 24 to 36 hours old. Therefore, the authors conclude, unless the sequence of histological changes in thrombi is very much delayed in atheromatous coronary arteries, it would seem that coronary thrombosis is often not the cause, but the terminal event in the presence of an already established recent myocardial infarct. *M. C. Berenbaum*

Clinical and Anatomic Features in Five Hundred Patients with Fatal Acute Myocardial Infarction. K. T. LEE, W. A. THOMAS, E. R. RABIN, and R. M. O'NEAL. *Circulation*, **15**, 197, 1957.

The clinical and anatomical features of 500 cases of acute myocardial infarction coming to necropsy at the Washington University School of Medicine, St. Louis, Missouri, during the period 1910–54 are described. In 429 of these cases it was possible to date the time of infarction. There was a preceding history of angina pectoris in half this number, and in the other half fatal myocardial infarction occurred without previous warning. Almost half the patients had evidence of old myocardial infarction in addition to a recent infarct, although only 25 per cent gave a history of past infarction. Chest pain was present in 64 per cent of the 429 patients. In 19 per cent of the whole series with recent infarction a correct diagnosis was not made in life. *James W. Brown*

Rupture of Papillary Muscles: Occurrence of Rupture of the Posterior Muscle in Posterior Myocardial Infarction. R. J. SANDERS, K. T. NEUBUERGER, and A. RAVIN. *Dis. Chest*, **31**, 316, 1957.

The authors present clinical and necropsy details of 5 cases in which death occurred, as the result of rupture of a papillary muscle complicating myocardial infarction.

Rupture of a papillary muscle usually occurs 3 to 17 days after the onset of symptoms of myocardial infarction shown electrocardiographically to be situated posteriorly. Clinically, there is a sudden onset of dyspnœa with signs of peripheral circulatory collapse and rapidly progressive pulmonary œdema. A harsh systolic apical murmur makes its appearance, or one previously present becomes accentuated, though sometimes it cannot be heard because of very loud respiratory noises. Death usually occurs from left ventricular failure with intractable pulmonary œdema. The prognosis is poor.

Only one case in the present series was diagnosed ante mortem, but the authors consider that it should be possible to differentiate rupture of a papillary muscle from acute cardiac dilatation and from rupture of the interventricular septum. In the latter event the systolic murmur is parasternal rather than apical, conduction defects are often present, and the electrocardiogram shows changes of anterior infarction. *Marcel Malden*

Limited Use of Anticoagulants in Acute Myocardial Infarction. Analysis of One Thousand "Good-risk" Cases. H. I. RUSSEK and B. L. ZOHMAN. *J. Amer. med. Ass.*, **163**, 922, 1957.

The authors have studied the mortality and incidence of thrombo-embolic complications in 1000 "good-risk" cases of acute myocardial infarction, which were not treated with anticoagulants. The series consisted of two

groups: (1) 489 cases selected and studied in retrospect; and (2) a further 511 cases selected for study at the time of their first examination. All patients were treated conservatively with 3 to 4 weeks' bed rest and leg exercises from the onset.

In Group 1 the over-all mortality was 3·1 per cent, mortality after the first 48 hours 1·7 per cent; and incidence of thromboembolism 0·8 per cent. In Group 2 the figures were 3·5 per cent, 1·8 per cent, and 3·7 per cent respectively. Thrombo-embolic incidents in the latter group were all mild in degree, with no deaths, and no case of cerebral or peripheral arterial embolism occurred. In the combined series there were 33 fatal cases (3·3%), in only 9 of which anticoagulant treatment might have saved life (3 deaths from recurrent thrombosis, one from cerebral embolism, and 5 from unknown causes). Of the remainder, 16 deaths occurred unexpectedly during the first 48 hours, 4 were from non-cardiac causes, and 4 were from rupture of the left ventricle. Thus death from thrombo-embolic causes occurred in less than 1 per cent of good-risk cases.

On the basis of these findings, and in view of the risk of hæmorrhagic complications and of the adverse effect of the disturbance to the patient inseparable from treatment with anticoagulants in hospital, the authors consider that the use of these drugs is contraindicated in good-risk cases of acute myocardial infarction, though this conclusion does not detract from their established value in properly selected cases. *V. Reade*

Effect of Heparin on Lipemia-induced Angina Pectoris. P. T. KUO and C. R. JOYNER. *J. Amer. med. Ass.*, **163**, 727, 1957.

The effect of heparin on acute anginal pain induced by administration of a fatty meal in patients with coronary arterial disease and old myocardial infarction was studied at the Hospital of the University of Pennsylvania, Philadelphia. A total of 15 attacks of angina were induced in 7 patients after a latent period of 5 to 5½ hours. In 14 of the 15 attacks subjective relief was obtained 5 to 15 minutes after heparin administration, and this was confirmed objectively by improvement in the electrocardiogram, ballistocardiogram, and pneumogram. Similar but less permanent improvement was obtained with glyceryl trinitrate. Plasma turbidity and serum total fatty acid values rose sharply after the meal until heparin was given, and then fell suddenly. The serum lipoprotein pattern also showed considerable anodal migration after heparin. No such changes occurred when the pain was relieved by glyceryl trinitrate, and there were no changes in the serum cholesterol and phospholipid levels. No objective or subjective improvement followed intravenous injection of saline solution.

J. Warwick Buckler

Serum Transaminase Determinations as a Diagnostic Aid in Myocardial Infarction. R. SHABETAL, A. IGLAUER, and D. M. ANDERSON. *Brit. med. J.*, **1**, 555, 1957.

The level of activity of glutamic oxalacetic transaminase in the serum was estimated in 4 groups of patients at the Jewish Hospital, Cincinnati. In 20 patients, none of whom was "suspected of a recent thrombo-embolic incident", the serum transaminase level was within the normal range of 10 to 40 units when estimated by Karmen's method.

Of 39 patients with suspected coronary arterial disease, 13 had clinical and electrocardiographic features typical of myocardial infarction. In 12 of these the serum transaminase level was raised. On the other hand 12 patients who on admission were suspected on clinical and electrocardiographic grounds of myocardial infarction, but in whom serial transaminase estimations gave normal results, were subsequently considered on other grounds not to have had infarctions. Raised serum transaminase levels were found in patients with congestive failure and a large liver, with cirrhosis, and with acute pancreatitis.

The serum transaminase level is normal for 6 to 10 hours after a myocardial infarction, reaching a peak 12 to 24 hours after the onset of pain and returning to normal within a week. Its estimation is useful in distinguishing the cardiac pain of ischæmia from that of infarction, but it is important to obtain blood samples within a few hours of the onset of pain.

D. Emslie-Smith

Serum Enzymes—I. Serum Lactic Dehydrogenase in Myocardial Infarction. L. P. WHITE. *New Engl. J. Med.*, **255**, 984, 1956.

The determination of serum levels of glutamic oxalacetic transaminase (G.O.T.), recently introduced as an aid in the differentiation of myocardial infarction and pulmonary infarction or embolism, suffers from three main defects: (1) abnormal levels of the enzyme persist only for 24 to 72 hours after the infarction occurs; (2) some patients with infarction of limited extent do not show abnormal levels of enzyme; and (3) the method is laborious. As the heart is rich in other enzymes, the practicability of utilizing the serum level of one of these has therefore been investigated. The enzymes thus studied were lactic dehydrogenase, aldolase, and hexose isomerase, the serum levels of which were determined and compared with that of G.O.T. in 50 patients in whom the diagnosis of myocardial infarction was entertained.

It was found that the serum level of lactic dehydrogenase was a good, if non-specific, index of the presence of myocardial infarction. Serum G.O.T. determination on the other hand appeared to be of little use in differentiating myocardial infarction, but was of help in the diagnosis of hepatitis. The superiority of lactic dehydrogenase determination depends on the simplicity of assay and on the greater degree and longer duration of the rise in level of this enzyme in the serum. Lactic dehydrogenase, in common with many other enzymes, is widely distributed throughout the body. Any cause of tissue destruction, such as infection, trauma, or infarction, may be associated with abnormal elevation of serum enzyme levels. *L. A. Elson*

HEART: 1909 – 1958

Nearly fifty years have passed since *Heart* was started, for the first number was published in July 1909. James Mackenzie and Thomas Lewis played the main part in this, and Lewis has recorded that Mackenzie asked him to accept editorial responsibility. Lewis was then 28. During the next 24 years, sixteen volumes appeared at somewhat irregular intervals, for Lewis was anxious to include only papers that reached his high standard, and as editor he was a beneficent dictator, with the friendly support of the late Mr. Morten Bond, Chairman of Shaw and Sons, the publishers.

It is right that this should be commemorated for, though *Heart* no longer exists as such, it is continued as *Clinical Science*, the title to which Lewis changed it in 1933, and less directly as the *British Heart Journal*, which started six years later. The last number of *Heart* contains papers by five present members of the British Cardiac Society apart from Frank Wilson and Lewis himself —Fraser, Grant, Cookson, Wayne, and Pickering. Some of those responsible for starting the *British Heart Journal* hoped that the title Heart might continue and might be used for it. This was discussed with Lewis, who finally agreed that it should be if the publishers were willing, but they thought it inadvisable at that time.

Archives des Maladies du Cœur et des Vaisseaux was started in 1908, the year before *Heart*, by Henri Vaquez: he was interested in diseases of the blood also, and the original title included *et du Sang*, but was shortened to its present form when, after the death of Vaquez in 1937, it was taken over by Laubry. *Zentralblatt für Herzkrankheiten* also was started in 1909 and was edited by M. Herz. The attitude to heart disease was changing and much new work was being done. Though there were many at work and along different lines, it is right to mention Mackenzie's work and his *Study of the Pulse*, published in 1902, as important landmarks.

It was a period of expansion in many directions. The Association of Physicians was founded in 1907; the *Quarterly Journal of Medicine* started that year and the *Archives of Internal Medicine* in 1908. Physicians were feeling two needs—to meet in larger national societies, and at the same time to divide according to their interests in the growing special branches. But beneath the smooth surface of scientific advance and progressive Liberalism that seemed likely to spread over the whole world, there were hidden dangers. Europe was nearing the end of a great era. Fortunately, the cataclysmic social and political changes that resulted from the First World War did not delay for long further scientific advances.

The *British Heart Journal*, as such, was started in 1939 by the British Cardiac Society, which had been in existence since 1922 and had recently changed from a small informal society, the Cardiac Club, to one that tried to embrace all those working in cardiology. In the same way, the *American Heart Journal* was started in 1925 by the American Heart Association which had been formed in 1923 and was a purely medical society until 1946, when it became a voluntary public health agency also. In Germany, Deutsche Gesellschaft für Kreislaufforschung, which has I think more professors of physiology and related sciences than most other cardiac societies, was founded in 1927 by B. Kisch and by A. Weber, who is still working in the Institute at Bad Nauheim, where the Society meets regularly: E. Stadler and B. Kisch were the first editors of *Zeitschrift für Kreislaufforschung* which was started the same year as Volume XIX, replacing the earlier *Zentralblatt für Herzkrankheiten* (1909–26). In France, the journal came first by many years, for the Société Française de Cardiologie was founded in 1937, nearly twenty years after the journal and through its editorial committee. In Italy also, *Cuore e Circulazione*, which was started in 1924

with C. Pezzi as editor, came many years before the cardiac society. Since 1916 there had been an earlier journal *Malattie di cuore*. The Gruppo Cardiologico Italiano was founded in 1935 and the Associazione Italiana di Cardiologia in 1947, and it was only in 1956 that the present Società Italiana di Cardiologia was founded.

Cardiologia was published at Basle in 1937 and has been the official journal of the Swiss Society of Cardiology since 1948—the year in which it was founded—and also of the Swedish Society since 1948 and of the Netherlands Society since 1949. *Acta Cardiologica* was started at Brussels in 1946 by La Société Belge de Cardiologie, which had been founded in 1934.

There are now many journals dealing with the heart and circulation but the writer has mentioned only some of those in English, French, or German. Others include *Revista Argentina de Cardiologia* (1934), *Arquivos Brasileiros de Cardiologia* (1948), *Indian Heart Journal* (1949), and recently *Sistole* from Montevideo. *Circulation* (1950), and *Circulation Research* (1953) are recent additions in the U.S.A. and show how rapidly the number and size is increasing. Readers and editors alike, pondering on the massive bulk of medical journals that constantly demands new library shelving, must earnestly hope that authors will cultivate the virtue of brevity.

When *Heart* was started in 1909 it was the first journal in Britain and one of the first in the world to be devoted entirely to cardiology, but a journal for neurology came much earlier. *Brain* was started in 1879 and has continued successfully with classic contributions from most of the great British neurologists; three of the four original editors were Fellows of the Royal Society, and ten of the contributors to the first volume are well-known names, even to a cardiologist. It is surprising that neurology should have acquired its special journal so early, only one year after Langley had founded the *Journal of Physiology* in 1878—a journal that will surely rank high for the number of classical papers that it has published and for the standards that it has set.

These are, of course, very recent dates compared with some scientific journals even among the biological sciences, for the *Philosophical Transactions of the Royal Society*, which contained many early medical contributions, has been published regularly since 1665. Medical papers in the 18th century were often published in the transactions of clinical or pathological societies, both in London and in the provinces, and in the following century in the special journals of medical schools and hospitals.

The association between Sir Thomas Lewis and the *British Heart Journal* was enhanced by the foreword he wrote for our first number. He recorded shortly the great names in British Cardiology, and from his wide experience gave advice to authors on how they should write. The Editors hope that every contributor will study this short foreword, for Lewis maintained that his own clear concise style was not a natural gift, but one that had been acquired by hard work in writing clearly and exactly what he meant, and in pruning away every redundant word.

We are glad to join with our sister journal, *Clinical Science*, in commemorating the fiftieth anniversary of the foundation of *Heart*, and in paying tribute to the great discoveries of James Mackenzie and Thomas Lewis and those who worked with them fifty years ago.

MAURICE CAMPBELL

LOUIS GALLAVARDIN

On December 2, 1957, at Lyons, Louis Gallavardin, aged 83, died peacefully in his sleep after a brief illness. A great pioneer in cardiology has departed, and as one who had enjoyed his friendship for over thirty years it is my sad privilege to give some account of him.

Born in Lyons in 1875, Gallavardin was trained in the Lyons Medical School, becoming *Interne* in 1895, and *Médecin des Hôpitaux de Lyon* in 1902, at the early age of 27. As an interne he was a contemporary of Alexis Carrel with whom he remained a lifelong friend. Of his teachers, Tripier influenced him most and he often spoke with admiration of Bouveret.

From 1898 to 1945, Gallavardin published 360 papers covering the whole field of cardiovascular disease with the exception of congenital malformations which except for aortic stenosis never interested him much. Written at a time when cardiology was advancing with rapid strides and attracting many new disciples to its ranks, these papers soon established Gallavardin's reputation as a leader of cardiology in Europe.

A list of his publications shows that up to 1910 he was still concerned with general medicine, though there was an early paper with Josserand (1901) on heart failure in young subjects due to primary myocarditis; this gave the first clear clinical and pathological account of a rare form of heart disease which later received much attention under the name of isolated or Fiedler's myocarditis. After 1910 his interests became centred on cardiovascular disease, and he must have been one of the first physicians in Europe to devote himself to the practice of cardiology.

At the start of the century, early models of the Riva-Rocci type of sphygmomanometer were coming into regular use, in spite of some opposition from physicians who still held the erudite finger to be the best pressure gauge. At first only the systolic pressure could be recorded, but with the advent of the auscultatory method (Korotkoff, 1905) and the Pachon oscillometer (1909), it became possible to estimate the diastolic pressure also. Gallavardin was an early worker in this field and his book *La Tension artérielle en Clinique*, first published in 1910 with the second enlarged edition in 1920, was for long the standard work on the measurement of blood pressure; its remarkably complete bibliography makes it still a valuable source of reference.

He was by nature and choice a clinician rather than a laboratory worker, but from the first he appreciated the great importance of electrocardiography, acquiring one of the original Cambridge cardiographs which was still in use when I visited him in 1926. He was a great admirer of Mackenzie whose work stimulated his interest in the arrhythmias, and from 1912 onwards Gallavardin applied himself to their methodical investigation, using a paper camera with the Cambridge electrocardiograph for this purpose. He acquired a vast collection of records of every sort of abnormal rhythm, many of which were reproduced in his papers. It was in Lyons that Bouveret wrote his classic description of paroxysmal tachycardia (1889) and it was natural for Gallavardin to interest himself in this form of arrhythmia, about which he made many valuable contributions, including statistics of 177 cases in 1930. He made a particular study of ventricular tachycardia, identifying a relatively benign form with frequent ventricular extrasystoles. Many of his observations were embodied in the book published in 1932 by Froment, who gave us some account of the work of the Lyons School in the *British Heart Journal* of 1953.

Gallavardin was interested in aortic stenosis and was the first to emphasize the frequency of a type that was not rheumatic "qui se caractérise par sa tendance particulière à réaliser le rétrécissement aortique pur et que cette cause doit être recherchée en dehors des atteintes rhumatismales franches ou frustes." He published a series of papers (1909, 1921, and 1936) and in the last described 50 such patients: he emphasized the frequent occurrence of effort syncope in this disease. Though this type is now generally regarded as congenital, the accuracy of his general picture has not been questioned.

In 1921, Gallavardin described paroxysmal pulmonary œdema in mitral stenosis, and in 1934 published his notable paper *Le rétrécissement mitral œdemateux* in which he clearly delineated a form of mitral disease that was then little known but is now recognized as the form that above all others demands surgical relief.

LOUIS GALLAVARDIN
1875–1957

He made a lifelong study of angina pectoris of which he acquired a vast experience in practice, and his modest treatise, *Les Angines de Poitrine* (1925), contains one of the best clinical descriptions of the anginal syndrome ever written. He was far too logical a thinker ever to be lured from the narrow path of proven facts by Allbutt's plausible aortic hypothesis, and never doubted that coronary disease was the most important cause of anginal pain.

Gallavardin's published work was not his main achievement. Almost single-handed, and at a time when Vaquez's clinic dominated cardiology in France and indeed in Europe, he founded a new and independent school of cardiology in Lyons. From the start this school has been served by its own men, trained in Lyons, men such as Gravier, Veil, and Froment, and including today Leon Gallavardin and Jean Gravier, who have followed in their fathers' footsteps.

Gallavardin was a great clinician and a master of observation at the bedside where nothing seemed to escape him, and I still retain a vivid recollection of his ward rounds at the ancient Hôtel-Dieu Hospital: first a penetrating interrogation of the patient, next a rapid yet meticulous examination, then a lucid but concise summing up, and finally the dictation of a brief but most illuminating summary of his conclusions for the notes. In clarity of thought and in ability to focus his mind straight on to the kernel of any problem, he reminded one of Lewis. His whole working life was spent in Lyons and in his later years he showed little inclination to leave his home town. He became President of the Société Française de Cardiologie in 1946, but I believe that he needed firm persuasion from Laubry to accept this honour which involved frequent sojourns in Paris.

He was much interested in paintings, miniatures, Persian art, and fine editions, and yet he was a man of simple habits, neat and punctilious in dress, precise and almost brusque in speech, quick but unhurried at work. I am sure that he would wish no better description of himself than that which he gave of Gravier: "le fidèle représentant du médecin hospitalier lyonnais" and so let us think of him with honour and affection.

D. EVAN BEDFORD

Selected Bibliography

General

1901. (With Josserand, E.) De l'asystolie progressive des jeunes sujets par myocardite subaigue primitive. *Arch. gén. Méd.*, **188**, 513 and 684.
1910. *La Tension artérielle en Clinique, sa Mesure, sa Valeur séméiologique.* Paris. 2nd edition in 1920.
1921. Symptômes et diagnostic de l'infarctus du myocarde. *J. Méd. Lyon*, **2**, 911.
1925. *Les Angines de Poitrine.* Paris.

Aortic Stenosis and Syncope on Effort

1909. Du rétrécissement aortique non-rhumatismal des jeunes sujets et de son analogie avec le rétrécissement mitral de Duroziez. *Lyon méd.*, **112**, 189.
1921. Le rétrécissement pur non-rhumatismal des jeunes sujets. *Presse méd.*, **29**, 224. Also, in 1936. *J. Méd. Lyon*, **17**, 593.
1933. Les syncopes d'effort. *Lyon méd.*, **151**, 217.

Paroxysmal Tachycardia

1912. Tachycardie paroxystique angineuse. *Lyon méd.*, **118**, 320.
1922. Extra-systolie ventriculaire à paroxysmes tachycardiques prolongés. *Arch. Mal. Cœur*, **15**, 298.
1930. (With R. Froment.) La tachycardie paroxystique: maladie de Bouveret, d'après une statistique de 177 observations. *J. Méd. Lyon*, **11**, 617.
1932. R. Froment. *Les Tachycardies paroxystiques ventriculaires.* Masson et Cie, Paris.

Mitral Stenosis and Pulmonary Œdema

1921. De l'œdème pulmonaire aigu dans les cardiopathies valvulaires endocardiques en dehors de la gravidité; insuffisance ventriculaire gauche et insuffisance auriculaire gauche. *Arch. Mal. Cœur*, **14**, 262.
1934. Le rétrécissement mitral œdemateux. *J. Méd. Lyon*, **15**, 609.

HÆMODYNAMIC CONSEQUENCES OF CORONARY HEART DISEASE

WITH OBSERVATIONS DURING ANGINAL PAIN AND ON THE EFFECT OF NITRO-GLYCERINE

BY

OTTAR MÜLLER AND KARL RØRVIK

From the University Institute for Respiratory Physiology (Dept. III) and Department VIII, Ullevaal Hospital, Oslo

Received October 22, 1957

It is known from previous investigations (Lewis *et al.* 1953) that patients with coronary heart disease, previous myocardial infarction, and an enlarged heart may show the usual signs of left ventricular failure with increased pulmonary vascular pressures and a tendency to reduced cardiac output. To our knowledge, no systematic investigations of cardiac output and pressures in the lesser circulation have been made in patients with coronary heart disease and a normal-sized heart, with anginal pain as the main symptom. Nor have any observations been published from the same patients when free from pain and when complaining of pain, either spontaneous or induced by exercise.

It is generally believed that the administration of nitro-glycerine leads to a dilatation of coronary vessels. An increase in coronary blood flow subsequent to nitro-glycerine has been demonstrated in animals (Gregg, 1950), and its effect on anginal pain due to coronary heart disease in man has also been attributed to its influence on the coronary blood flow (Wayne and Laplace, 1933; Russek *et al.*, 1955). However, there are no observations by cardiac catheterization on the effect of nitro-glycerine on the left ventricular function and the lesser circulation in man. This research has been designed to fill these apparent gaps.

Material and Methods. Twenty-four patients with coronary heart disease have been studied by cardiac catheterization, one of them twice at an interval of a year (observations 8 and 9); 20 had electrocardiographic signs and a history of previous myocardial infarction. In these patients catheterization was performed from one month (in one) to eight years after the last known infarction. The four patients without known infarction all had typical anginal pain and also cardiographic changes of angina on staircase tests.

The age of the patients, 3 of whom were women, varied from 45 to 84 years. In 3 (Cases 2, 7, and 24) the blood pressure had been raised but was, as in the others, normal at the time of the investigation. Cases 3 and 7 had diabetes mellitus, Cases 8 and 24 had xanthomatosis, and Case 24 had thrombocytopenia. All had regular sinus rhythm during the investigations.

With the patients resting on the table, pressure in the right atrium, pulmonary artery, and pulmonary artery wedge position (pulm. capillary pressure) were recorded. The oxygen consumption was determined by spirometry, using room air. Blood samples were obtained from the pulmonary artery (mixed venous blood) and from a peripheral artery, usually the brachial, by an indwelling needle.

The patients were investigated during exercise as well as at rest in 15 instances. The exercise consisted of bicycling in recumbency on an ergometer for at least 5½ minutes in 10 cases, but in the other 5 it had to be discontinued after 2½ to 4 minutes because of excessive dyspnœa or anginal pain. A Statham strain-guage coupled to an AC-DC amplifier and a Brush oscillograph was used for the pressure recordings, and the pressures related to a point 10 cm. in front of the patient's back. Manometric (van Slyke) and spectrophotometric (Refsum *et al.*, 1956) methods were used for the oxygen determinations in the blood samples. Cardiac output was determined according to the direct Fick principle and expressed in litres per minute per square meter body surface (cardiac index).

Results

(*a*) *Patients with dyspnœa but no angina.* Eight patients with previous infarction and with dyspnœa as the main complaint were selected for studies (Table I). Four of them were observed during moderate exercise as well as at rest. All had experienced nocturnal attacks of breathlessness, though in Case 1 this occurred only in combination with tachycardia (? paroxysmal). All showed enlarged hearts by X-ray (more than 500–540 ml./m.^{2} for men; Amundsen, 1956), except Case 3 with a heart size at the upper limit of normal.

TABLE I

Patients with Dyspnœa as the Main Symptom and with Enlarged Hearts

No.	Age	Heart vol. in ml./m.^{2}	Rest						Exercise				
			O_2 cons. ml./m.^{2}	CI	RAP_m	PAP_m	PCP_m	MVB O_2%	Incr. O_2 cons.	CI	PAP_m	PCP_m	MVB O_2%
1	49	600	150	4·4	5	(RV 36/4)		74·0					
2	58	590	155	3·1	4	31	25	57·0					
3	60	510	145	2·5	4	25		63·0					
4	75	LV+	160	4·2	9	34	25	69·3					
5	61	670	165	1·8	9	35	19	59·7	180	1·9	45	35	42·0
6	63	760	160	3·5	6	40	32	60·0			62	45	51·1
7	61	650	150	4·3	4½	27	17	64·7	300	4·3	51	39	52·5
8	53	650	160	2·9	6	34	27½	69·1	400	4·0	60	37½	51·1

All patients were men except Case 4. All had nocturnal dyspnœa. O_2 cons.=Oxygen consumption, ml. per minute per square metre body surface. RAP_m, PAP_m, RCP_m=Mean right atrial, pulmonary arterial, and pulmonary capillary pressures in mm. Hg. MVB O_2%=Oxygen saturation of mixed venous blood. Incr. O_2 cons.=Increase of oxygen consumption during exercise, ml. per minute. CI=Cardiac Index. Case 6: Exercise 50 kg. m./min. for 2½ minutes.

In all six patients where pulmonary capillary pressure was obtained, this was increased above normal limits (14 mm. Hg) even at rest, with a parallel increase in pulmonary artery pressure. Two others (Cases 1 and 3) showed right ventricular and pulmonary artery pressures just above the upper limit of normal. Although only one (Case 5) has a subnormal cardiac index, five showed resting oxygen saturation in mixed venous blood below 65 per cent. The right atrial mean pressure tended to be high, being 6 mm. Hg or more in four, while in two, who had the smallest hearts, it was within normal limits.

In four patients exercised, pulmonary capillary pressures increased still further and ranged from 35 to 45 mm. Hg. In one (Case 6) where it reached the highest level, the exercise test had to be discontinued after 2½ minutes because of excessive dyspnœa although the effort was very moderate. In two of three cases where cardiac output was measured, no increase occurred during exercise.

(*b*) *Angina with previous myocardial infarction.* Eleven patients with previous myocardial infarction and with anginal pain as the dominant symptom were catheterized, 8 of them during exercise as well as at rest (Table II). Six had experienced nocturnal attacks of anginal pain, the remainder only on varying degrees of effort. All except one had X-ray examination, and all these showed heart volumes below or within the upper limit of normal.

Only one (Case 9) of ten patients had an abnormally raised pulmonary capillary pressure at rest. Five, however, had pressures in the upper, normal region (11–12 mm. Hg). None had subnormal cardiac outputs, but two (Cases 15 and 17) had a cardiac index near the lower, normal limit for their age (Brandfonbrener *et al.*, 1955). One man, 84 years old, in whom no determination of oxygen

TABLE II

PATIENTS WITH ANGINAL PAIN AS THE MAIN SYMPTOM AND AN EARLIER INFARCTION AND A NORMAL-SIZED HEART

No.	Age	Ang. pain	Heart vol. in ml./m.²	Rest						Exercise						
				O_2 cons. ml./m.²	CI	PAP_m	PCP_m	MVB O_2%	Heart rate	Incr. O_2 cons.	CI	PAP_m	PCP_m	MVB O_2%	Heart rate	A.P
9	52	+++	500	160	3·3	24	16	69·0	68							
10	84	+++			(A-Vd. 4·9)	13		58·0	70							
11	53	+++	420	175	5·0	22	6	69·2	85							
12	64	+++	390	140	4·9	19	11	77·0	67	450	5·2	43		52·3	100	+?
13	59	+++	360	150	3·9	18	12	73·5	75	510		45	32		106	+
14	59	+++	280	145	3·7	17	9	71·9	75			40	33	59·1	96	+
15	66	++	460	140	2·8	19	12	65·9	62	280	4·0	32	25	58·6	80	+
16	49	++	510	145	3·0	25	11	69·9	62			35		59·9	95	−
17	63	++	450	140	2·6	18	11	67·0	60			41	27	59·2	70	+
18	45	++	450	130	3·3	15	8	70·0	75	250	4·9	25	14	61·9	86	−
19	46	+	435	135	3·0	17	10	71·0	62	335	4·4	27	(20) 15	59·3	83	−

All patients were men. The work was 110 kg. m./min. for Case 14, 90 kg. m./min. for Case 16, and 60 kg. m./min. for Case 17. It was done for 5½ minutes by Case 16 and for 3 minutes by the other two. Ang. pain=history of anginal pain, +=pain on heavy effort only, ++=pain on slight to moderate effort, +++=Angina decubitus. A.P.=Anginal pain during the exercise test. See also legend Table I.

consumption was obtained, was the only patient in the group with an oxygen saturation in mixed venous blood below 65 per cent: an arterio-venous oxygen difference of 49 ml./l. did not, however, suggest an abnormally low cardiac output for his age.

Of the 8 patients exercised, 6 showed abnormal increases of the pulmonary vascular pressure, with an increase in pulmonary capillary pressure in the four where this was recorded. All except one of these experienced typical or probable anginal pain during the exercise test.

Two patients only had normal or near normal hæmodynamics at the end of the exercise period: neither had a constricting sensation in the chest during the test. In one (Case 19) pulmonary capillary pressures increased to 20 mm. during the first two minutes of exercise, but thereafter declined steadily and measured 15 mm. at the end of the six minutes of exercise.

In distinction to those with an enlarged heart and dyspnœa as the main symptom, all patients in this group showed an increase in cardiac output during exercise, as judged from cardiac index, arterio-venous oxygen difference, or oyxgen saturation in mixed venous blood.

(*c*) *Angina without recognizable infarction.* Three patients with coronary heart disease and anginal pain, but without known infarction were observed at rest and during exercise (Table III). All three had normal hæmodynamics at rest. The rather low cardiac index in Case 20 is normal for the patient's age according to Brandfonbrener *et al.* (1955)

All patients, however, developed an abnormally raised pulmonary capillary pressure during exercise. Only one of the three experienced constricting pain during the test. The heart rates increased only moderately. Only one exercised for a period long enough to obtain data for cardiac output determination (Case 21; CI, 4, 2). The arterio-venous oxygen difference in the others did not suggest an abnormal cardiac output response to exercise.

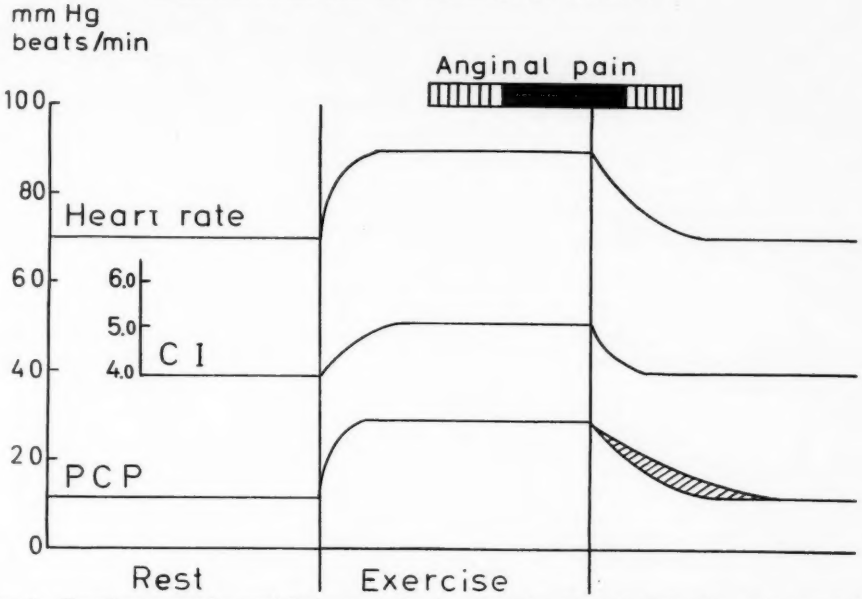


FIG. 1.—Reaction to exercise precipitating anginal pain. Patients with earlier infarctions and normal-size hearts. Schematic drawing based on observations from Cases 12, 13, 14, 15, and 17.

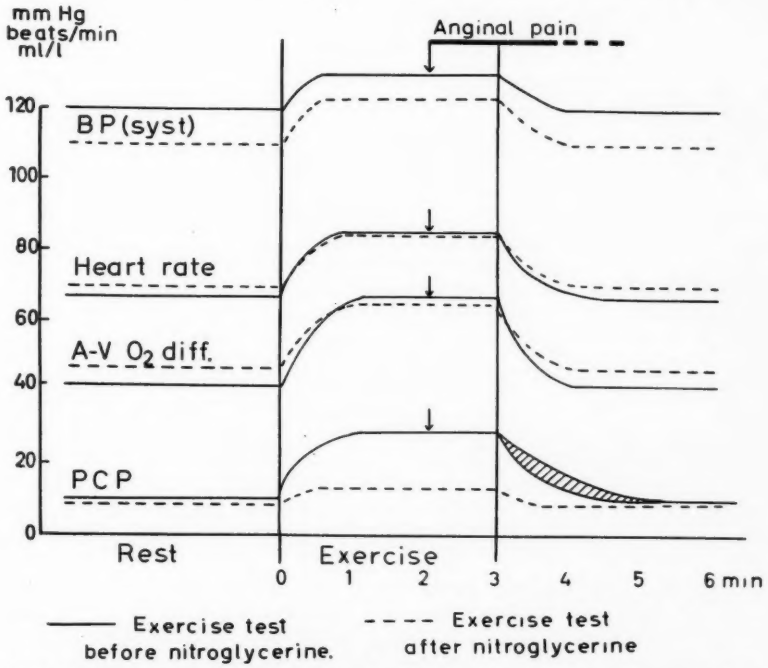


FIG. 2.—Reaction to exercise before and after nitro-glycerine. Patients with normal-sized hearts. Schematic drawing based on observations from Cases 14, 17, and 22.

(*d*) *Spontaneous attacks of anginal pain.* Two patients, both women, one with and one without known infarction, were observed at the height of a spontaneous attack of anginal pain when resting on the table (Table IV). Both had a heart of normal size. Both had subnormal hæmoglobin concentrations, one being treated with anticoagulants and the other having thrombocytopenia. Both had normal pulmonary vascular pressures when free of pain and at rest. During the attack of anginal pain both showed gross increases of pulmonary capillary pressures. Simultaneously, rises in heart rate of about 15 beats a minute occurred, together with an increase in oxygen saturation of mixed venous blood indicating an increase of cardiac output of 20–25 per cent if the oxygen consumption remained unchanged. During a similar attack in one of them (Case 24) the systolic peripheral blood pressure was observed to increase by 25 mm.

TABLE III

PATIENTS WITH ANGINAL PAIN AS THE MAIN SYMPTOM BUT WITHOUT AN EARLIER INFARCTION

No.	Age	Ang. pain	Heart vol. in ml./m.^{2}	Rest						Exercise					
				O_2 cons. ml./m.^{2}	CI	A-V O_2 d.	PAP_m	PCP_m	Heart rate	A-V O_2 d.	PAP_m	PCP_m	BP incr.	Heart rate	A.P.
20	72	+	460	115	2·3	5·1	16	10	50	7·5	37	28		72	–
21	55	+++	370	130	3·1	4·3	15	6	75	5·8	21	16	25	80	–
22	50	++	380	125	3·5	3·5	14	10	66	6·6	34	28	15	88	+

All patients were men. Exercise was between 80 and 90 kg. m./min. for 3, 6, and 3 minutes respectively. A-V O_2 d. =Arterio-venous oxygen difference, volume per cent. BP incr.=Increase of palpatory systolic systemic blood pressure, mm. Hg. See also legend Tables I and II.

TABLE IV

SPONTANEOUS ATTACKS OF ANGINAL PAIN

No.	Age	Heart vol. in ml./m.^{2}	Patients free from pain						During anginal pain			
			O_2 con. ml./m.^{2}	CI	MVB O_2%	PAP_m	PCP_m	Heart rate	MVB O_2%	PAP_m	PCP_m	Heart rate
23	46	400	145	3·7	60·3	13	8	75	66·3		35	93
24	66	350	125	3·0	64·8	25	14	77	72·2	43	34	92

Both patients were women. Case 23 had a Hb. of 64%, an old infarct, and xanthomatosis. Case 24 had a Hb. of 79%. See legend to Tables I and II.

(*e*) *Effect of nitro-glycerine.* Four patients, two with and two without myocardial infarction, were observed at rest and during exercise, before as well as 10 to 14 minutes after the administration of 0·5 mg. of nitro-glycerine (Table V). All four had anginal pain as the main symptom, a normal-sized heart, and ST–T depression after standard staircase tests.

All patients had normal or near normal hæmodynamics at rest. No systematic changes were observed at rest after nitro-glycerine, except that the pulmonary capillary pressure, which had been normal, showed a fall of 1–2 mm. in all patients and the peripheral systolic blood pressure declined 0–10 mm.

During the exercise test before nitro-glycerine all four patients developed abnormally increased pulmonary capillary pressures, 16 mm. in the only patient without anginal pain, 27, 28, and 33 mm. in the three who developed constricting pain during the test. In these three, the pain appeared after 2–2½ minutes of bicycling. The abnormal increase in pulmonary capillary pressures, however,

TABLE V

EFFECT OF NITRO-GLYCERINE IN PATIENTS WHOSE MAIN SYMPTOM WAS ANGINAL PAIN

No.	Age sex	Heart vol. in ml./m²		Rest						Exercise						
				CI	A-V O_2 d.	PAP_m	PCP_m	Heart rate	BP (s)	A-V O_2 d.	PAP_m	PCP_m	Heart rate	Work load	BP (s)	A.P.
14	59 m.	280	Before	3·7	3·7	17	9	75	140	6·7	40	33	96	110 3	150	+
			After		4·6	15	7	69	135	6·7	21	11	97	115 3	155	−
17	63 m.	450	Before	2·6	5·4	18	11	60	115	7·0	41	27	70	60 3	125	+
			After		5·3	18	9	62	105	6·7	23	13	68	60 3	110	−
21	55 m.	370	Before	3·1	4·3	15	6	75	110	5·8	21	16	80	85 6	135	−
			After		4·4	12	4	88	105	6·1	17	7	75	90 6	130	−
22	52 m.	380	Before	3·5	3·5	14	10	66	100	6·6	34	28	88	80 3	115	+
			After		4·2	16	9	78	100	6·1	19	14	86	90 3	105	−

Cases 14 and 17 had previous cardiac infarction and the other two had not. BP (s)=Palpatory systolic systemic blood pressure, mm. Hg. Work load=Kg. m./min. The duration of exercise was 3 minutes in all except Case 21 where it was 6 minutes. See also legends Tables I and II.

was present after only one minute of exercise. In Case 22 the pain increased in intensity for 2–3 minutes after the exercise was stopped and nitro-glycerine administered: during this period the mean pulmonary artery pressure continued to increase and reached a maximum of 52 mm. with a diastolic pressure of 42 mm. The pressures did not fall to the level before exercise until 6 minutes after the exercise was stopped.

During the same or slightly increased exercise 10 to 14 minutes after the administration of nitro-glycerine, the pulmonary capillary pressure remained within normal limits in all four patients. The arterio-venous oxygen difference was remarkably similar before and after nitro-glycerine in three of the four, indicating similar trends in cardiac output. In the fourth a smaller oxygen difference suggested a higher cardiac output during the second exercise test. The heart rates were also remarkably constant. The dose of nitro-glycerine was not such as to lower the arterial pressure significantly, and in fact the systolic arterial pressure rose with exercise in all cases.

DISCUSSION

Our observations in the group of patients with previous infarction, an enlarged heart, and dyspnœa as their main symptom are in accord with the findings of previous investigators (Lewis *et al.*, 1953). Signs of left ventricular failure with increased pressures throughout the lesser circulation and a tendency to subnormal cardiac outputs were found at rest, with much greater deviations from normal during exercise. In all cases exercised, pulmonary capillary pressures rose to levels where pulmonary œdema is imminent (Gorlin *et al.*, 1951), and no increase in cardiac output occurred in two of the three.

In contrast to the above group, most patients with previous infarction, a heart of normal size, and varying degrees of anginal pain showed essentially normal hæmodynamics at rest and when free of

pain. The only exceptions were a man of 84 with a subnormal resting oxygen saturation in mixed venous blood, but with an arterio-venous oxygen difference suggestive of a normal cardiac output for his age, and a patient with a borderline heart size and a pulmonary capillary pressure just above the upper limit of normal. All the others in this group had normal pulmonary capillary pressures, though five of the nine were in the upper normal region, and had normal cardiac outputs for their ages.

Similar, essentially normal findings were obtained at rest and when free from pain in patients with varying degrees of anginal pain as the main complaint, but without known infarction. The transition of a patient from one group to the other in the course of a year without a new, major infarction is illustrated in Table VI. With an increase in pulmonary vascular pressures and a fall, albeit small, in cardiac output, there was a change in symptoms from mainly pain and only slight dyspnœa on effort, to dyspnœa both on effort and at night with only slight pain, and an increase in heart volume.

The observations during exercise in patients with hearts of normal size were essentially similar whether they had a history or signs of previous infarction or not: signs of varying degrees of left ventricular failure with raised pulmonary capillary and/or arterial pressures were observed in nine of eleven patients exercised. The nine with signs of left ventricular failure comprised all patients who experienced anginal pain during the exercise test together with three who did not. In patients where anginal pain was precipitated, the rise in pulmonary capillary pressure was observed to precede the sensation of pain which usually appeared after two or three minutes of exercise, while the rise in pressure was recorded after one minute.

TABLE VI

OBSERVATIONS ON A PATIENT, ONE AND TWO YEARS AFTER MYOCARDIAL INFARCTION

After infarct	Pain		Dyspnœa		Heart vol. in ml./m.^{2}	Rest			
	Noct.	On effort	Noct.	On effort		O_2 cons.	CI	PAP_m	PCP_m
1 year	+	++	−	+ −	500	160	3·3	24	16·0
2 years	−	+	+	++	600	160	2·9	34	27·5

See legend to Tables I and II.

Neither of the two patients without signs of left ventricular failure (indicated by increased pulmonary capillary pressures) at the end of the exercise period, experienced anginal pain during the test. One of them (Case 19) developed a raised pulmonary capillary pressure during the first two minutes of exercise. The pressure, however, thereafter declined and approached the upper limit of normal at the end of the exercise period.

In all cases with a normal-size heart the cardiac output response to exercise seemed to be within normal limits as judged from cardiac index, arterio-venous oxygen difference, and oxygen saturation in mixed venous blood, irrespective of whether there was failure of the left ventricle or not.

The two patients observed at the height of a spontaneous attack of anginal pain both showed transitory, gross signs of left ventricular failure with increase of pulmonary capillary pressures up to levels where pulmonary œdema may develop (Gorlin *et al.*, 1951). It seems therefore that the anginal state generally is combined with varying degrees of left ventricular failure, whether the pain is precipitated by effort or is spontaneous. If precipitated by effort, it is usually preceded by the signs of left ventricular failure, which may also develop without any constricting sensations.

A slight fall in pulmonary capillary pressure (1–2 mm. Hg) was the only systematic alteration observed in the lesser circulation 10 minutes after nitro-glycerine was given to four patients with normal heart sizes—when resting on the table. During exercises, however, the changes in hæmodynamics before and after nitro-glycerine were striking. Before nitro-glycerine was given all four

patients developed abnormally raised pulmonary capillary pressures and signs of left ventricular failure during exercise. After nitro-glycerine they all tolerated the same or slightly heavier work without abnormal rise in pulmonary capillary pressures. In face of the same or slightly increased amount of work performed, the unaltered or slightly reduced arterio-venous oxygen differences observed exclude any significant decrease in cardiac output during the second exercise test. The same holds true for stroke volume as the heart rates also were nearly constant. The pulse pressures in the left ventricle may—in cases without mitral valvular stenosis—be gauged by taking the difference between the pulmonary capillary pressure and the systolic pressure in the peripheral arteries (Epps *et al.*, 1953; Werkö *et al.*, 1953; and Goldberger *et al.*, 1957). It will be noted that this remained constant or even increased. These observations—the unchanged or slightly increased cardiac output, stroke volume, and pressure generated by the left ventricle—together seem to exclude a reduced effective forward left ventricular work or stroke work during the second exercise test as compared to the first. Thus the reduced pulmonary capillary pressure in exercise could not be the consequence of any decline in left ventricular load. Accordingly, the administration of nitro-glycerine, leading in these four cases to a greatly reduced left atrial—and hence left ventricular diastolic—pressure without a simultaneous reduction of effective forward left ventricular work and stroke work, seems to have altered materially the relationship between the amount of left ventricular work and the left ventricular diastolic filling pressure necessary to perform it.

Sarnoff *et al.* (1954) reported the observation of a depressive effect on the left ventricular function curve ("Starling curve") of artificial reduction of the blood flow in the left main coronary artery in dogs. As nitro-glycerine is supposed to exert its influence on the myocardium through an augmentation of coronary blood flow (Gregg, 1950), our observations from patients before and after the administration of this drug seem to parallel the findings of Sarnoff *et al.* The hæmodynamic changes therefore suggest a reserve of coronary vascular capacity reacting to nitro-glycerine with great influence on the function of the left ventricle. Whether nitro-glycerine causes an exceptional dilatation of vessels of normal calibre or the relaxation of abnormal vasoconstriction cannot be decided from the findings reported here.

Conclusions

Twenty-four patients with coronary heart disease, without signs of valvular disease or any rise of blood pressure, have been studied by cardiac catheterization.

Patients with coronary heart disease, previous myocardial infarction, and an enlarged heart, and with dyspnœa as the main symptom generally show hæmodynamic signs of left ventricular failure at rest, with striking accentuation on moderate effort.

Patients with anginal pain as their main complaint and with a heart of normal size mostly have normal hæmodynamic findings at rest when free from pain, whether they have had an old infarct or not. Even if the effective, forward left ventricular stroke work is only moderately increased, anginal pain, whether spontaneous or after exercise, is accompanied by signs of left ventricular failure. This develops before the pain is felt, and in some cases without any constricting sensation. It may continue and even increase after the precipitating factor is removed. Patients in this group usually show normal cardiac output response to moderate exercise, even when left ventricular failure develops (Fig. 1).

In patients with anginal pain as the main symptom and with a heart of normal size, no major alterations occur in the essentially normal hæmodynamics of the lesser circulation subsequent to nitro-glycerine, when the patient is resting and at ease. During moderate exercise after nitro-glycerine there are no systematic changes in cardiac output, effective forward left ventricular work, or stroke work, but the same amount of exercise that before the administration of the drug precipitated gross left ventricular failure may be tolerated with no signs of pulmonary venous hypertension (Fig. 2).

Nitro-glycerine appears to improve the work capacity of the left ventricle, possibly by increasing coronary blood flow.

The authors are greatly indebted to Prof. S. A. Jervell and C. Müller for the unfailing interest during the work and to Prof. J. McMichael for his valuable advice during the preparation of the paper.

REFERENCES

Amundsen, P. (1956). *Second Europ. Congr. Cardol., Stockholm, Abstracts of Papers*, p. 38.
Brandfonbrener, M., Landowne, M., and Shock, N. W. (1955). *Circulation*, **12**, 557.
Epps, R. G., and Adler, R. H. (1953). *Brit Heart J.*, **15**, 298.
Goldberger, H., Dickens, J., Raber, G., and Hayes jr., E. (1957). *Amer. Heart J.*, **53**, 579.
Gorlin, R., Lewis, B. M., Haynes, F. W., Spiegel, R. J., and Dexter, L. (1951). *Amer. Heart J.*, **41**, 834.
——, Sawyer, C. G., Haynes, F. W., Goodale, W. T., and Dexter, L. (1951). *Amer. Heart J.*, **41**, 192.
Gregg, D. E. (1950). *Coronary Circulation in Health and Disease*. Philadelphia.
Lewis, B., Houssay, H. E. J., Haynes, F. W., and Dexter, L. (1953). *Circ. Research*, **1**, 312.
Refsum, H. E., and Sveinsson, S. L. (1956). *Scand. J. clin. Lab. Invest.*, **8**, 67.
Russek, H. I., Urbach, K. F., and Zohman, B. L. (1955). *J. Amer. med. Assoc.*, **158**, 1017.
Sarnoff, S. J., and Berglund, E. (1954). *Circulation*, **9**, 706.
Wayne, E. J., and Laplace, L. B. (1933–34). *Clin. Science*, **1**, 103.
Werkö, L., Varnarnauskas, E., Eliasch, H., Lagerloef, H., Senning, A., and Thomasson, B. (1953). *Circ. Research*, **1**, 337.

THE DIAGNOSTIC USE OF AN EAR OXIMETER IN CONGENITAL HEART DISEASE

BY

C. R. WOOLF, W. PAUL, AND R. W. GUNTON

From the Departments of Medicine and Pathological Chemistry, University of Toronto, and the Medical Service, Toronto General Hospital, Toronto, Canada

Received July 19, 1957

The ear oximeter can serve two purposes in the investigation of congenital heart disease. It can provide a continuous record of arterial oxygen saturation and its changes in response to varying situations; it can inscribe a dye dilution curve of the central circulation following intravenous injection of the dye, Evans Blue (T–1824), from which the direction and magnitude of intra-cardiac shunts can be estimated. These two functions of the oximeter in the study of congenital heart disease have been described and developed by the Mayo Clinic group (Burchell and Wood, 1948; Nicholson *et al.*, 1951; Swan *et al.*, 1953; Broadbent and Wood, 1954); and by Gilmore *et al.* (1954).

The increase in cyanosis during exercise of patients with cyanotic congenital heart disease has long been observed clinically (Abbott, 1936) and more recently has been measured quantitatively as fall in arterial oxygen saturation by the oximeter (Montgomery *et al.*, 1948; Ferguson *et al.*, 1949*a*; Burchell *et al.*, 1950; Van Lingen and Whidborne, 1952). This phenomenon is characteristic of patients with a central veno-arterial shunt, but does not distinguish them from patients with acquired heart disease or severe pulmonary disease, who may show a considerable fall of arterial oxygen saturation during exercise. Almost all previously reported studies have been carried out with the patient breathing room air; little attention has been paid to changes in arterial oxygen saturation when patients perform an exercise test while breathing 100 per cent oxygen (Ferguson *et al.*, 1949*b*; Burchell *et al.*, 1950).

It is the purpose of this paper to show that a decrease in arterial oxygen saturation during a standard exercise test while the subject is breathing pure oxygen occurs in the presence of a central veno-arterial shunt, but not in acquired heart disease or severe pulmonary disease. This test, used together with central dye dilution curves of Evans Blue has been found valuable in the routine investigation of congenital heart disease.

METHOD

The direct writing ear oximeter and its use in recording changes in arterial oxygen saturation have been described elsewhere (Paul, 1953, 1955; Woolf *et al.*, 1956).

With the ear oximeter in place the patient was required to step up and down a 20-cm. step thirty times in one minute and then rested until the arterial oxygen saturation had returned to its usual level. He then breathed 99·8 per cent oxygen from a Boothby-type mask and when the arterial oxygen saturation had reached a steady state the exercise test was repeated.

After a period of rest in the supine position, dye injection was then made into an ante-cubital vein. A volume of 4 ml. of Evans' Blue dye solution (20 mg.) was injected over a period of 1·5 to 2·0 seconds and was followed by 5·0 ml. of saline solution through the side-arm of a Y connection. The patient continued to breathe oxygen during inscription of the dye curve to prevent the minor fluctuations in arterial oxygen saturation encountered in patients breathing room air. In the interpretation of dye curves the principles outlined by Swan *et al.* (1953) and Broadbent and Wood (1954) have been followed.

In the normal curve shown in Fig. 2A, dye, which has passed through the heart and lungs and out into systemic arteries, appears at the ear 11 seconds after the beginning of the injection. There is then a rapid upstroke to the peak concentration. The time from first appearance of dye to peak concentration has been designated "Build-up time" (BT) (Wood and Swan, 1954). Following the peak there is a rapid fall in dye concentration, forming a disappearance slope as the dye moves past the ear. This part of the curve never reaches the base line because it is interrupted by dye returning to the ear after a complete circulation to cause a second small peak concentration of recirculating dye. The disappearance slope of the primary curve may be extrapolated to intersect with the base line. The time from peak concentration to this intersect has been designated "Disappearance time" (DT).

In right-to-left shunt (Fig. 2B) some of the dye is carried with venous blood to the left side of the heart by-passing the lungs; this dye appears early at the ear, forming an initial peak concentration. Dye that has traversed the lungs produces a second peak concentration. This "double-hump" contour is characteristic of central veno-arterial shunt. Assuming complete mixing of dye with venous blood proximal to the shunt and utilizing the Hamilton principle that blood flow is proportional to the area of dilution curves of the central circulation, Swan *et al.* (1953) have calculated from dye curves the percentage of systemic venous blood which is shunted to the left side of the heart.

In left-to-right shunts (Fig. 2D) the appearance time and upstroke of the dye curve are normal. The peak concentration is lower than expected, but the characteristic features are the prolongation of the disappearance time, and absence of a clearly defined recirculation peak. In left-to-right shunts part of the dye that has traversed the lungs will pass into the systemic arteries, producing the initial normal part of the curve. The other part of the dye will pass through the shunt and through the lungs again. Part of this shunted dye that has passed through the shorter pulmonary circuit will appear earlier at the ear than the dye that returns from the systemic circulation. A succession of rapid recirculations accounts for the slow prolonged disappearance slope. The curve of left-to-right shunts may be distinguished from the curve of low cardiac output (Fig. 4C) by analysis of the ratio of disappearance time (DT) to build-up time (BT). BT is relatively short in left-to-right shunt, and prolonged in low cardiac output. DT/BT ratios greater than 2·0 suggest a left-to-right shunt (Broadbent and Wood, 1954).

Material

The patients were divided into 4 groups.

Group I (14 cases): Congenital heart disease with a right-to-left shunt.

Group II (12 cases): Non-cyanotic congenital heart disease.

Group III (10 cases): Acquired heart disease.

Group IV (20 cases): Pulmonary disease severe enough to cause a significant fall of the arterial oxygen saturation on exercise.

The age, sex, and diagnosis of all patients are shown in Tables I and II. The diagnosis was made by clinical and routine radiological examination. In addition, cardiac catheterization was carried out on all patients with congenital heart disease, selective angiocardiography on some, and the diagnosis was confirmed by the findings at operation in several of them. All patients in Group I were shown to have a right-to-left shunt by methods other than those under review in this study. Respiratory function tests were done on all patients with pulmonary disease (vital capacity, maximum breathing capacity, spirogram tracing; and in some cases residual volume and total lung-capacity).

Results

These are summarized in Tables I and II.

Group I. All patients with a right-to-left intracardiac shunt showed a fall of the arterial oxygen saturation on exercise while breathing air and an equal or greater fall when the test was repeated while breathing oxygen (Fig. 1B). The normal response to exercise, breathing air, and breathing oxygen, is shown in Fig. 1A. In normal subjects there may be a small fall of arterial oxygen saturation on exercise breathing air (Woolf *et al.*, 1956), but there is no fall when breathing oxygen.

The dye curves showed the characteristic short circulation time and double hump pattern (Fig. 2B).

TABLE I

THE AGE, SEX, DIAGNOSIS, CHANGES IN ARTERIAL OXYGEN SATURATION DURING EXERCISE, BREATHING AIR AND OXYGEN, AND TYPE OF DYE CURVE IN PATIENTS WITH CONGENITAL HEART DISEASE

	Patient	Age	Sex	Diagnosis	Decrease in per cent oxygen saturation of arterial blood during exercise		Dye curve type
					Breathing air	Breathing 99·8 per cent oxygen	
Group I R→L shunt	R.L.	15	M	Tetralogy of Fallot	17·5	18·5	R→L
	D.N.	28	M	Tetralogy of Fallot; lung cyst	13·3	21·0	R→L
	N.C.	27	F	Tetralogy of Fallot; kyphoscoliosis	21·2	33·4	R→L
	N.P.	29	F	Tetralogy of Fallot; after Brock opn. for pulmonary stenosis	23·7	23·7	—
	N.F.	31	F	Atrial septal defect; pulmonary stenosis	8·5	9·5	R→L
	J.C.	16	F	Atrial septal defect; pulmonary stenosis	9·4	9·6	R→L
	M.T.	24	F	Atrial septal defect; pulmonary stenosis	11·8	9·9	R→L
	B.B.	25	F	Atrial septal defect; pulmonary hypertension	11·8	12·4	R→L
	I.N.	33	F	Atrial septal defect; pulmonary hypertension	13·3	14·3	R→L
	V.M.	28	F	Ventricular septal defect; pulmonary hypertension	21·7	22·0	R→L
	J.B.	28	F	Ventricular septal defect; pulmonary hypertension	18·4	18·8	R→L
	W.C.	21	F	Tricuspid atresia	8·0	9·0	Abnormal
	C.L.	27	F	Common truncus	24·8	39·3	R→L
	A.M.	40	F	Reversed shunt: ductus arteriosus	7·8	2·6	Normal
Group II Non-cyanotic congenital heart disease	I.W.	54	F	Atrial septal defect	8·1	0	L→R
	W.C.	46	M	Atrial septal defect	0	0	L→R
	A.D.	26	F	Atrial septal defect	2·6	0	L→R
	G.B.	53	F	Atrial septal defect	1·3	0	L→R
	D.C.	27	F	Atrial septal defect	0·8	0	L→R
	H.L.	22	M	Ventricular septal defect	1·0	0	L→R
	I.M.	28	F	Pulmonary stenosis	0·8	0	Normal
	R.W.	15	M	Pulmonary stenosis	1·6	0	Normal
	M.E.	32	F	Patent ductus arteriosus	2·2	0	L→R
	J.H.	35	M	Patent ductus arteriosus	2·2	0	L→R
	M.L.	42	F	Patent ductus arteriosus	0	0	Normal
	H.W.	20	M	Patent ductus arteriosus	2·6	0	? Normal

In one patient (A.M.) with patent ductus arteriosus, pulmonary hypertension and reversal of shunt, there was only a slight fall of the arterial oxygen saturation on exercise, breathing oxygen, even with the oximeter on the left ear (Fig. 3B). This was due to the sampling site, the ear supplied by the left carotid artery, being proximal to the site of the veno-arterial shunt. The dye curve was normal in form (Fig. 4B).

Group II. The patients with acyanotic congenital heart disease showed varying degrees of arterial oxygen desaturation on exercise, breathing air, and no fall on exercise, breathing oxygen (Fig. 1D and 3A).

The dye curves showed the pattern of left-to-right shunt in the patients with atrial septal defect (Fig. 2D) and ventricular septal defect, and in two of those with patent ductus arteriosus. The dye curves were normal in pulmonary stenosis and in the other two cases of patent ductus arteriosus (Fig. 4A).

Group III. Patients with acquired heart disease showed a variable fall of the arterial oxygen saturation on exercise, breathing air, and there was no fall of the arterial oxygen saturation on exercise breathing oxygen (Fig. 3C).

The dye curves showed a prolonged circulation time in the presence of heart failure and the contour of a low cardiac output (Fig. 4C).

Group IV. The patients with pulmonary disease all showed a significant fall of arterial oxygen saturation on exercise breathing air, but in only one case was there a fall on exercise breathing oxygen, and this fall was barely measurable. In some patients there was mainly a ventilatory defect (J.F., Fig. 5C), in others mainly a diffusion defect (J.I., Fig. 5B), and in others a combination of factors (Fig. 5A).

TABLE II

THE AGE, SEX, DIAGNOSIS, AND CHANGES IN ARTERIAL OXYGEN SATURATION DURING EXERCISE, BREATHING AIR AND OXYGEN, OF PATIENTS WITH ACQUIRED HEART DISEASE AND PULMONARY DISEASE

	Patient	Age	Sex	Diagnosis	Decrease in per cent oxygen saturation of arterial blood during exercise	
					Breathing air	Breathing 99·8 per cent oxygen
Group III Acquired heart disease	F.D.	28	F	Mitral stenosis	1·8	0
	H.B.	36	F	Mitral stenosis	2·0	0
	C.S.	48	M	Mitral stenosis	0·7	0
	G.L.	47	M	Mitral stenosis	0·5	0
	F.G.	21	F	Mitral and aortic stenosis, and regurgitation	1·0	0
	V.C.	35	F	Mitral and aortic stenosis, and regurgitation	0	0
	R.S.	15	M	Aortic regurgitation	0	0
	M.S.	64	M	Aortic regurgitation	0	0
	V.E.	26	M	Primary pulmonary hypertension	2·8	0
	D.V.	33	M	Constrictive pericarditis	5·4	0
Group IV Pulmonary disease	J.F.	19	F	Kyphoscoliosis	8·0	0
	M.R.	42	F	Inactive tuberculosis; thoracoplasty	11·2	0
	R.H.	46	M	Emphysema	6·3	9
	B.W.	54	M	Emphysema	5·8	0
	C.G.	63	M	Emphysema	14·7	0
	G.W.	55	M	Emphysema	6·2	0·7
	W.K.	60	M	Emphysema	7·3	0
	K.H.	49	M	Emphysema	6·7	0
	L.J.	55	M	Emphysema; asthma	10·3	0
	W.E.	61	M	Emphysema; asthma	14·7	0
	J.W.	68	M	Emphysema; pulmonary fibrosis	16·5	0
	K.S.	45	M	Emphysema; pulmonary fibrosis	8·9	0
	H.H.	53	M	Emphysema; pulmonary fibrosis	6·5	0
	J.Bl.	34	M	Pulmonary fibrosis	13·1	0
	G.C.	32	M	Pulmonary fibrosis	10·5	0
	J.I.	27	M	Berylliosis	12·6	0
	M.B.	37	M	? Sarcoidosis	17·4	0
	G.M.	39	M	? Sarcoidosis	7·5	0
	G.G.	33	F	Secondary carcinoma	4·3	0
	P.D.	38	F	Secondary carcinoma	5·8	0

DISCUSSION

Two reasons have been proposed to explain the decrease in arterial oxygen saturation on exercise in patients with a central veno-arterial shunt. On exercise, the blood returning to the right atrium (from active muscles) will have a lower oxygen content than in the resting state. Some of this blood will pass through the cardiac defect to the left side of the heart and reduce the arterial oxygen saturation. This could occur without any change in blood flow through the shunt (Burchell and Wood, 1948). A second explanation is that the proportion of venous blood shunted does in fact increase with exertion (Bing *et al.*, 1947; Hickam, 1949; Burchell *et al.*, 1950).

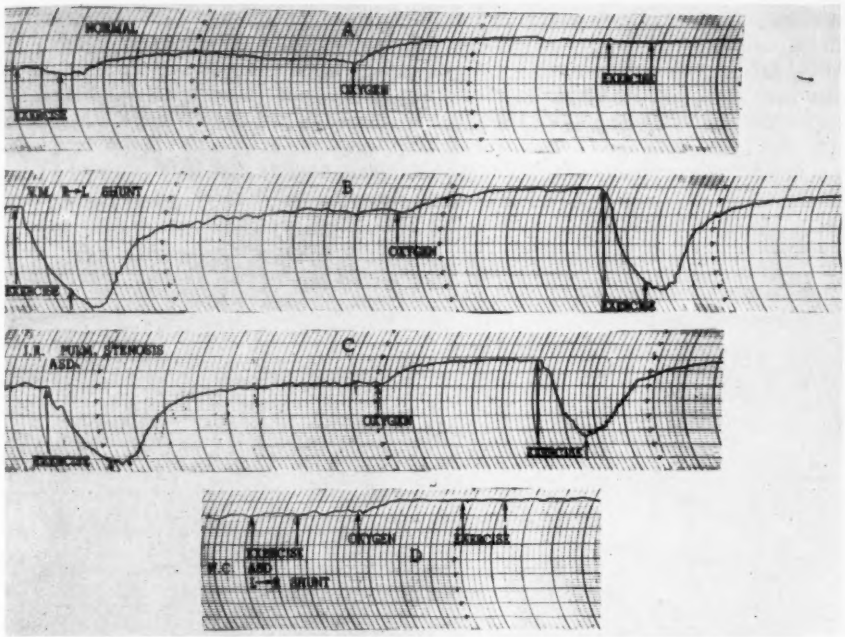


FIG. 1.—Changes in arterial oxygen saturation during exercise, breathing air and then breathing oxygen. To be read from left to right. A downward deflection of the record indicates a fall of arterial oxygen saturation, an upward deflection a rise. (A) Normal subject: slight fall on exercise when breathing air, but no fall when breathing oxygen. (B) Right-to-left shunt (ventricular septal defect and pulmonary hypertension): severe fall of arterial oxygen saturation on exercise when breathing air and when breathing oxygen. (C) Right-to-left shunt (atrial septal defect and pulmonary stenosis): this patient had a normal arterial oxygen saturation at rest. (D) Left-to-right shunt (atrial septal defect): no fall of arterial oxygen saturation during exercise breathing air or oxygen.

When the subject breathes pure oxygen, the shunted venous blood is not exposed to the increased oxygen tension in the pulmonary alveoli. The fall in arterial oxygen saturation should be as great as that produced by identical exercise when breathing air. This has been true in all the patients reported in this study. In three there was an even greater fall during exercise when breathing pure oxygen than during exercise breathing room air. The reason for this is not clear. It is possible that the general rise in arterial oxygen saturation at the start of oxygen breathing before exercise improved the patient subjectively so that he performed the test with more vigour, exaggerating the mechanisms producing the fall.

The absence of a fall in arterial oxygen saturation during exercise breathing pure oxygen served to distinguish the patients with a left-to-right shunt, acquired heart disease, and severe pulmonary disease from those with a right-to-left shunt. In the former group almost all the blood from the right side of the heart passes through lung tissue. The increase in alveolar oxygen tension, when pure oxygen is breathed, compensates for defects of circulation, diffusion, and ventilation.

In one patient with severe pulmonary emphysema (G.W., Table II), a slight fall of arterial oxygen saturation of 0·7 per cent was observed during exercise breathing oxygen. Using the criteria adopted from this study, a small central veno-arterial shunt was indicated by this observation. A true but minor shunt may have occurred from an unsealed foramen ovale associated with

pulmonary hypertension; or multiple small intra-pulmonary veno-arterial shunts, as described by Riley and Cournand (1949) in pulmonary disease, may have been demonstrated.

It would be expected that a patient with pulmonary arterio-venous aneurysm would show the same response as a patient with right-to-left intra-cardiac shunt. However, Hultgren and Gerbode (1954) have reported one case where there was no significant fall of arterial oxygen saturation on exercise while breathing air, and there was evidence that during exercise the flow through the fistula decreased while the flow through the pulmonary capillary bed increased.

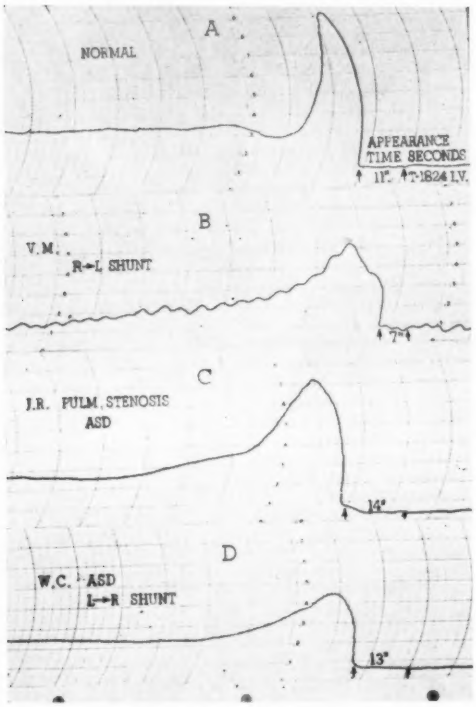


FIG. 2.—Evans' Blue dye curves of same patients as in Fig. 1. To be read from right to left. First arrow marks time of injection of Evans' Blue dye into arm vein. Patients at rest breathing pure oxygen. (A) Normal subject: rapid upstroke to the peak concentration followed by a rapid fall in dye concentration and then second small recirculation peak. (B) Right-to-left shunt: short appearance time, and double hump pattern as part of dye passes across ventricular septal defect and reaches ear sooner than dye that passes through pulmonary circulation. (C) Right-to-left shunt: just before the main upward deflection there is a slight rise due to a small right-to-left shunt at rest. There is some prolongation of the descent of the curve suggesting left-to-right shunt. Importance of R→L shunt in this case was shown by exercise test (Fig. 1). (D) Left-to-right shunt: normal appearance time and normal upstroke to low peak concentration. The descent of the curve is prolonged and there is no clearly defined late recirculation peak as in the normal (see text).

It is possible that very small right-to-left shunts may not be demonstrated by the exercise test performed during pure oxygen breathing. When a subject breathes 99·8 per cent oxygen from a mask, the amount of oxygen dissolved in physical solution in the plasma may be as great as 2·2 ml. per 100 ml. (Wood, 1949) and may be sufficient to saturate fully the hæmoglobin of small amounts of venous blood entering the left side of the heart through a septal defect. Suspicion that small right-to-left shunts may be missed by the exercise test performed during oxygen breathing is thus far speculative and based on failure to show arterial oxygen desaturation in five cases of uncomplicated atrial septal defect (Table I, Group II, Fig. 1D). Although in this condition the shunt is commonly considered to be entirely left to right, Hickam (1949), and Calazel *et al.* (1951) had reported that small right-to-left shunts may occur, and Swan *et al.* (1954) found small right-to-left shunts in three of five cases of uncomplicated atrial septal defect by injection of dye into the venæ cavæ. In the present study a right-to-left shunt was clearly demonstrated by the performance of exercise, while breathing pure oxygen, in five cases of atrial septal defect complicated by pulmonary stenosis or pulmonary hypertension (Table I, Group I, Fig. 1C). The test has been sensitive enough to detect a right-to-left shunt through a patent foramen ovale barely large enough to admit a small

dissecting probe, in a patient shown at necropsy to have pulmonary stenosis and an intact ventricular septum (Example 4).

The dye curves have shown characteristic early appearance time and "double hump" pattern in patients with large right-to-left shunts (Fig. 2B; Fig. 6), and smaller early deflections above the base line (Fig. 2C) in patients with small right-to-left shunts who did not have cyanosis or significant arterial oxygen unsaturation at rest. The characteristic early recirculation and gradual downstroke of a left-to-right shunt has always been found in patients with proven atrial and ventricular septal defect, but has not been as decisive in patent ductus arteriosus. Recirculation occurs later in patency of the ductus than in either septal defect and more nearly simulates the normal curve. Reversal of flow in patent ductus arteriosus cannot be demonstrated well by either dye curve or exercise test, because, even if the left ear is used, the left common carotid artery which supplies it is proximal to the usual site of entrance of the ductus into the aorta.

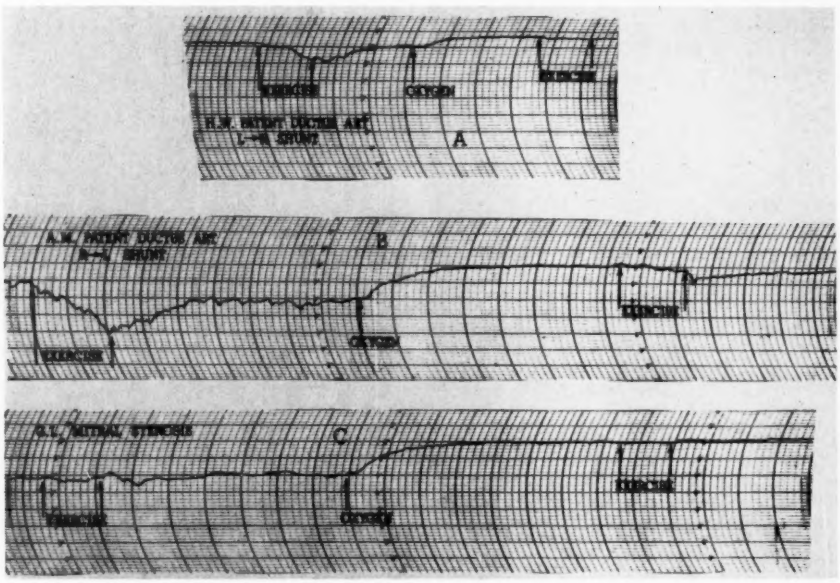


FIG. 3.—Changes in arterial oxygen saturation during exercise, first breathing air and then breathing oxygen. (A) Patent ductus arteriosus: note slight fall of arterial oxygen saturation when breathing air and no fall when breathing oxygen. A normal response not indicative of right-to-left shunt. (B) Patent ductus arteriosus with pulmonary hypertension and reversal of shunt: note fall of arterial oxygen saturation on exercise breathing air and a smaller fall when breathing oxygen. Indicates R→L shunt (see text). (C) Mitral stenosis: note slight fall of arterial oxygen saturation breathing air; no fall breathing oxygen; not indicative of R→L shunt.

Three stages in the progression of atrial septal defect are demonstrated by dye curves in Fig. 6. The characteristic early recirculation and gradual downstroke of a left-to-right shunt is present in uncomplicated cases. Pulmonary hypertension will cause first a bi-directional shunt and later, when right ventricular failure occurs, a more complete right-to-left shunt with obvious cyanosis and clubbing.

The oximeter tests described in this study are safe and simple to perform; they cause little discomfort and may be completed within thirty minutes. In cases where the clinical diagnosis is readily apparent and where cardiac catheterization is indicated to obtain quantitative information, their

value is supplementary. They can, however, serve two important purposes. First, they may be used as screening tests in patients suspected of having congenital heart disease, where cardiac catheterization would not normally be carried out because of absence of symptoms or doubtful clinical evidence of heart disease. Second, the oximeter tests may help the solution of difficult cases, even where a full cardiac investigation has been completed.

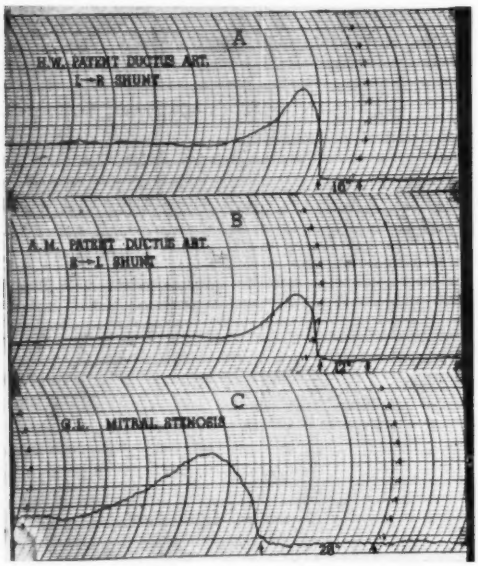


FIG. 4.—Evans' Blue dye curves of same patients as in Fig. 3. (A) and (B): Comparatively normal dye curves of patients with patent ductus arteriosus, irrespective of direction of the shunt (see text). (C) Mitral stenosis: Note prolongation of appearance time and slow ascent and slow descent of the curve, characteristic of low cardiac output.

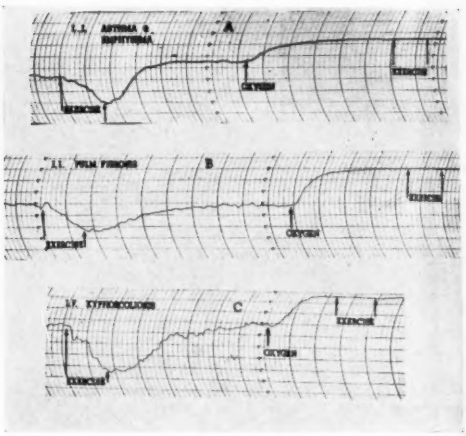


FIG. 5.—Changes in arterial oxygen saturation during exercise, first breathing air and then breathing oxygen, in patients with pulmonary disease. Note all have the same characteristics of a fall of arterial oxygen saturation, breathing air, and no fall of arterial oxygen saturation when breathing oxygen.

Examples. (1) When there is both a congenital heart lesion and a respiratory disability it is possible to decide whether the fall of arterial oxygen saturation during exercise, breathing air, is due to pulmonary insufficiency or to a veno-arterial shunt.

N.C., a 27-year-old housewife, had both a severe kyphoscoliosis and congenital heart disease. There was a severe fall of the arterial oxygen saturation on exertion breathing air. The presence of an even greater fall when breathing oxygen confirmed the clinical impression that the cyanosis was primarily due to a right-to-left shunt. The dye curve showed that a right-to-left shunt was present also at rest.

(2) To demonstrate the presence of bi-directional shunts.

J.R., a 27-year-old salesman, showed the clinical signs of pulmonary stenosis. At rest the arterial oxygen saturation was normal. The dye curve (Fig. 2C) showed a normal appearance time but a very small rise just before the main upward deflection. This suggested the possibility of a small right-to-left shunt at rest. There was slight prolongation of the descent of the curve, suggesting some left-to-right shunt. On exercise breathing air (Fig. 1C) there was a fall of arterial oxygen saturation of 24·1 per cent and when breathing oxygen a fall of 23·7 per cent. This clearly

illustrated that there was a considerable shunt of blood from right to left on exercise, probably through a septal defect.

(3) To distinguish acquired heart disease from congenital heart disease.

H.B., a 36-year-old housewife in congestive heart failure, was thought to have mitral stenosis, but the auscultatory, radiographic, and phonocardiographic evidence was indecisive. Right heart catheterization showed no left-to-right shunt, pulmonary artery pressure 75/40 mm. Hg, and wedge pressure 15 mm. Hg. Arterial oxygen saturation was 90 per cent, but she appeared clinically deeply cyanosed. There was indecision about valvotomy. Congenital heart disease (atrial septal defect) with R.→L. shunt was suspected. Dye curve and exercise test showed no R.→L. shunt. At operation tight mitral stenosis was demonstrated.

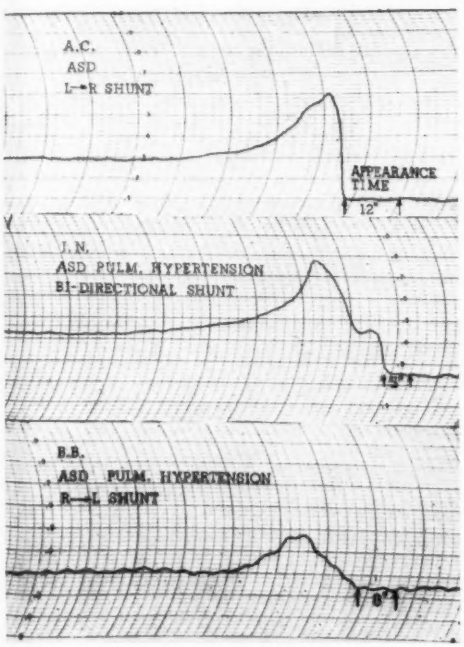


FIG. 6.—Dye curves in three patients with atrial septal defect. To be read from right to left. Top panel (A.C.) Characteristic L→R shunt pattern: normal appearance time, normal upstroke, early re-circulation, gradual downstroke. Middle panel (I.N.). Bi-directional shunt. Early appearance, distinct early circulation produced by part of dye passing direct from right atrium to left, gradual downstroke of L→R shunt. Lower panel (B.B.). Early appearance and double hump pattern of large R→L shunt. Oscillations in tracing are always found in pure R→L shunt, even with patient breathing pure oxygen and may represent respiratory variations in shunt.

(4) To aid in the selection of surgical treatment.

D.N., a 27-year-old housewife, had clinical evidence of infundibular pulmonary stenosis, confirmed by angiocardiography, which also demonstrated a right aortic arch, but showed no early appearance of dye in aorta. Cyanosis and clubbing were questionable; arterial oxygen saturation at rest was 91 per cent. The right ventricle could not be entered at cardiac catheterization and the pressure in that chamber was unknown. In the discussion of surgical treatment it was put forward that the patient had several features of Fallot's tetralogy, but probably had ventricular septal defect with equal pressure in the two ventricles, without over-riding aorta. It was feared that infundibular resection alone (Brock) might create a left-to-right shunt through the ventricular septal defect and would be less desirable than an open heart procedure, which would allow the septal defect to be repaired. Dye curve and exercise tests demonstrated clearly a R.→L. shunt, but so small as to be hæmodynamically unimportant. The Brock operation was carried out but the patient did not survive. Post-mortem the ventricular septum was intact. An unsealed foramen ovale would just admit a small dissecting probe.

Summary

In the investigation of congenital heart disease an ear oximeter has been use to provide a continuous record of arterial oxygen saturation during exercise, with the patient first breathing air and then breathing pure oxygen. Dye dilution curves of the central circulation following intravenous injection of Evans' Blue dye have been recorded.

In the presence of a right-to-left shunt at rest the dye curves showed a short appearance time and a characteristic double hump form. With exercise there was a fall of the arterial oxygen saturation when breathing air and when breathing oxygen.

In the presence of a left-to-right shunt the dye curves showed a normal appearance time, a normal steep ascent, but prolongation of the descent and absence of a recirculation peak. With exercise there was a varying degree of fall of the arterial oxygen saturation while breathing air, but no fall when breathing oxygen.

In pulmonary disease severe enough to cause a significant fall of the arterial oxygen saturation during exercise while breathing air, there was no fall during exercise while breathing oxygen.

The oximeter tests have been valuable in detecting intra-cardiac shunts, in particular right-to-left shunt in the presence of a normal arterial oxygen saturation at rest. They have distinguished the cyanosis of right-to-left shunt from the cyanosis of pulmonary disease and acquired heart disease.

The authors wish to acknowledge the technical assistance of Miss Sylvia Davies and Mr. T. Nelberg and the financial support of the Ontario Heart Foundation. The use of the oximeter was made possible by the financial support of the Atkinson Charitable Foundation.

Addendum

A 42-year-old woman with an arteriovenous aneurysm of the upper lobe of the right lung (proved by angiopneumogram and operation) showed a fall of arterial oxygen saturation of 7 per cent on exercise while breathing air and a fall of 7 per cent whilst breathing oxygen.

References

Abbott, M. E. (1936). *Atlas of Congenital Cardiac Disease*. American Heart Association, New York.
Bing, R. J., (1951). *Bull. Johns Hopkins Hosp.*, **88**, 20.
—— Vandam, L. D., and Gray, F. D. (1947). *Bull. Johns Hopkins Hosp.*, **80**, 121.
Broadbent, J. C., and Wood, E. H. (1954). *Circulation*, **9**, 890.
Burchell, H. B., and Wood, E. H. (1948). *Mod. Concepts Cardiovas. Disease*, **17**, 25.
——, Taylor, B. E., Knutson, J. R. B., and Wood, E. H. (1950). *Circulation*, **1**, 404.
Calazel, P., Gerard, R., Daley, R., Draper, A., Foster, J., and Bing, R. J. (1951). *Bull. Johns Hopkins Hosp.*, **88**, 20.
Ferguson, J. K. W., Finlayson, D. M., and Hilliard, I. M. (1949*a*). *Federation Proc.*, **8**, 44.
——, ——, —— (1949*b*). Unpublished observations.
Gilmore, H. R., Hamilton, M., Kopelman, H., and Sommer, L. S. (1954). *Brit. Heart J.*, **16**, 301.
Hickam, J. B. (1949). *Amer. Heart J.*, **38**, 801.
Hultgren, H. N., and Gerbode, F. (1954). *Amer. J. Med.*, **17**, 126.
Montgomery, G. E., Jr., Wood, E. H., Burchell, H. B., Dry, T. J., Parker, R. W., and Helmholz, H. F. (1948). *Amer. Heart J.*, **36**, 668.
Nicholson, J. W., III, Burchell, H. B., and Wood, E. H. (1951). *J. Lab. clin. Med.*, **37**, 353.
Paul, W. (1953). *J. Scientific Instruments*, **30**, 165.
—— (1955). *J. Scientific Instruments*, **32**, 286.
Riley, R. L., and Cournand, A. (1949). *J. App. Physiol.*, **1**, 825.
Swan, H. J. C., Burchell, H. B., and Wood, E. H. (1954). *Circulation*, **10**, 705.
——, Zapata Diaz, J., and Wood, E. H. (1953). *Circulation*, **8**, 70.
Van Lingen, B., and Whidborne, J. (1952). *Circulation*, **6**, 740.
Wood, E. H. (1949). *J. App. Physiol.*, **1**, 567.
——, and Swan, H. J. C. (1954). *J. App. Physiol.*, **6**, 797.
Woolf, C. R., Gunton, R. W., and Paul, W. (1956). *Amer. Rev. Tuberc.*, **74**, 511.

THE DIAGNOSIS OF MITRAL INCOMPETENCE FROM LEFT ATRIAL PRESSURE CURVES

BY

BERTRAND G. WELLS

From St. Bartholomew's Hospital

Received August 12, 1957

Changes in the atrial pressure curves are known to occur in mitral or tricuspid incompetence. Although there are many reports of such changes there has been no attempt to determine whether they can indicate the degree of valvular incompetence that is present. The review of these reports has therefore been brief.

Mackenzie (1910) described changes in the venous pulse in tricuspid incompetence. These changes were confirmed by Wiggers (1923) and Bloomfield *et al.* (1946). McCord and Blount (1952) described an obliteration of the x descent by an early systolic pressure rise. They postulated that the height of the v wave should form a basis for the estimation of the severity of tricuspid incompetence.

The study of the changes in left atrial pressure in mitral incompetence is more recent. Wiggers and Feil (1922) described changes in the left atrial pressure curve in dogs when temporary mitral incompetence was produced. Similar changes were reported by Haring *et al.* (1956) who noted that there were slight differences between the wedge pressures and the true left atrial pressures. Despite these differences much of the study of left atrial pressure changes in man has been made from wedge pressure tracings.

Several workers have considered that a tall broad v wave is typical of mitral incompetence (Gorlin *et al.*, 1952; Wade *et al.*, 1952; Biörck *et al.*, 1953). Others have stressed the importance of the obliteration of the x descent (Lagerlöf and Werkö, 1949; Husfeldt and Warburg, 1952; Gérard and Benyamine, 1956). Dexter *et al.* (1950) felt that wedge pressure curves might indicate the degree of mitral incompetence. Finally it has been suggested (Owen and Wood, 1955) that the rate of y descent divided by the height of the preceding v wave might, by denying the existence of significant stenosis, indicate the presence of mitral incompetence.

On the other hand a number of workers have stated that the changes in wedge pressure tracings are of little value in determining whether or not there is significant mitral incompetence (Wynn *et al*, 1952; Venner and Holling, 1953; and Soulié *et al.*, 1954). Eliasch (1952) considered that a tall v wave did not always indicate mitral incompetence but might be due to pulmonary hypertension. Logan and Turner (1953) found that the shape of the wedge pressure curve did not help them to diagnose mitral incompetence. A similar view was held by Burchell and Edwards (1953). McGreggor and Zion (1955) described a case of almost pure mitral incompetence with a normal wedge pressure tracing.

The inaccuracies of wedge pressure tracings have been eliminated by direct puncture of the left atrium (Björk, 1955). Various results have been obtained in mitral incompetence. It has been stated (Kent *et al.*, 1955) that when the v wave exceeded the c wave by 5 mm. Hg or more there was mitral incompetence. Other studies (Musser *et al.*, 1956) have failed to confirm this. Bücherl (1956) described a single systolic peak with no x descent. Fox *et al.* (1956) describing pressure tracings taken at operation considered that mitral incompetence abolished the x descent and caused a very tall v wave with a steep descending limb.

Opinions thus differ as to whether mitral incompetence can be diagnosed from left atrial pressure curves, and the present study has been made to establish what correlation exists between the features of the left atrial pressure curve and the degree of mitral incompetence. The material has also been examined to see whether some modification or combination of the features already described would provide a better correlation.

Material and Method

Pressure tracings were taken at operation on seventy-seven patients with mitral valve disease. The surgeon was Mr. O. S. Tubbs or Mr. I. M. Hill. In most cases two observations were made on each patient, one before and one after valvotomy. Thus there were seventy-seven observations before valvotomy and seventy-three after. Fifty observations were on valves found to be incompetent and one hundred on valves showing no incompetence. The patients undergoing surgical treatment were consecutive, except for five observations on valves without incompetence which were omitted in order to obtain a round figure of 100 for the controls. All the patients had mitral stenosis which was relieved by valvotomy. In the fifty observations on patients with mitral incompetence, this was present before valvotomy in the majority and only occasionally was it produced by valvotomy: two of the six observations on valves with severe incompetence were made before valvotomy. One remained severe after valvotomy while the other became only moderate.

Needles were inserted into the left atrium and the left ventricle after thoracotomy and pressure curves with synchronous electrocardiogram were taken with a Sanborn electromanometer and twin Viso-cardiette. The manometer was switched from the atrial to the ventricular needle allowing two heart beats to be recorded from each chamber before switching back to the other. In this way comparable cardiac cycles were obtained, which were superimposed with the help of the electrocardiogram by tracing onto transparent paper. The sensitivity used was 25 mm. Hg per cm. and the paper speed 25 mm. per second. In addition, a higher sensitivity (10 mm. Hg per cm.) was used to study the curves in greater detail. The baseline was recorded before and after the curves by holding the needle outside the centre of the chamber concerned. The pulmonary arterial pressure was measured in each patient by needle puncture.

The following measurements were recorded at each observation.

(1) The atrial pressure just preceding the a or c wave.
(2) The extent of rise of c wave.
(3) The atrial pressure at the x descent or, if this was absent, at the end of the first third of ventricular systole.
(4) The height of the v wave.
(5) The time from the onset of descent of the v wave to the nadir of the y descent.
(6) The level of the nadir of the y descent.
(7) The left ventricular systolic pressure.
(8) The pulmonary arterial pressure.

The surgeon palpated the mitral orifice at each observation and recorded the size of the opening and the degree of mitral incompetence present. The latter was described as none, very slight, slight, moderate, or severe. These were termed respectively grades 0 to 4.

Results

The material was first analysed according to the criteria suggested by previous workers. The height of the v wave, the v–c difference, and the Ry/v ratio were determined and each was contrasted with the degree of mitral incompetence found.

The height of the v wave is clearly of little importance if it is measured as an absolute pressure, for it would be elevated in pure mitral stenosis with a high left atrial pressure. The v wave was therefore measured from the atrial pressure immediately preceding the a or c wave. This was not

necessarily the lowest atrial pressure in ventricular diastole for there was occasionally a gradual rise between the y descent and the a or c wave. The results shown in Fig. 1 indicate that tall v waves do not necessarily indicate mitral incompetence and small ones do not necessarily indicate its absence.

The height of the v wave above the c wave (v–c difference) was next considered. Kent *et al.* (1955) suggested that figures of 5 mm. Hg or more indicated the presence of mitral incompetence. An analysis of the present series on these lines is shown in Fig. 2. The cases of severe mitral incompetence all showed a v–c difference of over 5 but so do many cases with little or no incompetence.

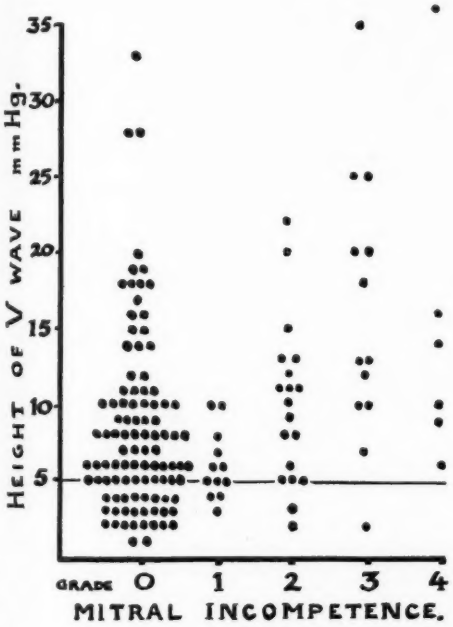


FIG. 1.—The height of the v wave was taken as the height of the apex of this wave above the atrial pressure just prior to the a or c wave. The grades 0 to 4 of mitral incompetence were assessed, by palpation of the mitral orifice, as none, very slight, slight, moderate, and severe. As all the observations were at operations for mitral stenosis none of the regurgitant streams was of the size found in pure mitral incompetence.

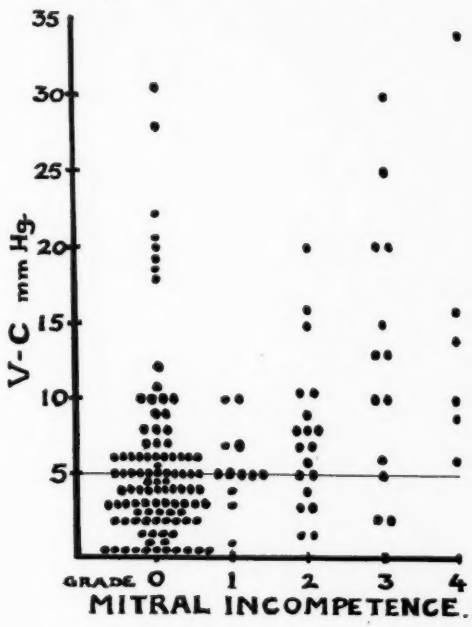


FIG. 2.—The "V–C difference" is the maximum height of the v wave minus the maximum height of the c wave. The grades of mitral incompetence are as for Fig. 1.

The Ry/v (Owen and Wood, 1955) was next calculated in each case and the results were compared with the degree of mitral incompetence in Fig. 3. A considerable number of those with pure stenosis had Ry/v ratios of over 1·6, and this method was therefore considered unsuitable for the diagnosis of mitral incompetence.

In the present series none of these methods has proved of much value in diagnosing mitral incompetence from atrial pressure tracings. The material was therefore examined to see whether any new criteria would be more helpful.

Although the peaks of the c and v waves do not help in the identification of mitral incompetence the fall between the two appears to be of greater significance. This x descent is sometimes abolished

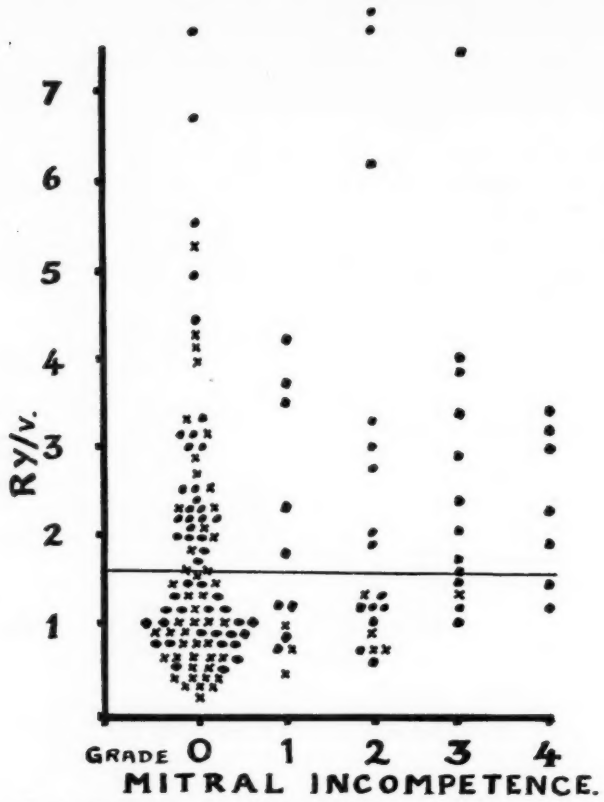


FIG. 3.—The Ry/v ratio is the height of the v wave above the y nadir divided by the product of the height of the v wave and the time between the beginning of the descent of the v, and the y nadir. A figure of 1·6 or over is said to deny the existence of significant stenosis. Those cases with mitral orifice area of under 1 sq. cm. (length × breadth) are marked with a cross. The grades of mitral incompetence are as for Fig. 1.

in mitral incompetence as is shown in Fig. 4. At other times it is present but reduced in size. In mitral stenosis without incompetence the x descent is often clear despite the presence of tall v waves, as is the case in Fig. 5. In other cases the x descent appears to be reduced because of the presence of a large c wave as can be seen in Fig. 6. Such a c wave is synchronous with the rise of ventricular pressure and must not be confused with the delayed rise of pressure that occurs in mitral incompetence (Fig. 4). This difference is important and can only be established when the pressure tracings are free from excessive damping.

The term "corrected x descent" has been used to describe the measurement made in this study. The x descent was measured when there was a distinct nadir at about the end of the first third of ventricular systole. When such a nadir was absent, the atrial pressure was measured at the end of the first third of ventricular systole. From the figure obtained was subtracted the atrial pressure just prior to the a or c wave, and also the height of the c wave (the number of mm./Hg of synchronous rise of atrial and ventricular pressure). The "corrected x descent" was occasionally a

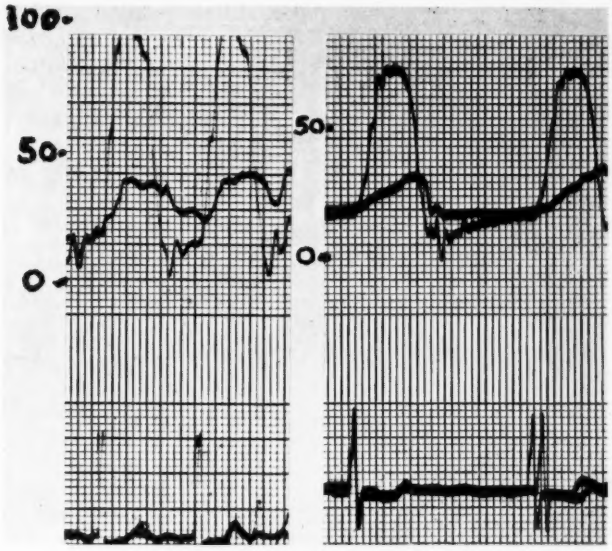


FIG. 4.—Superimposed atrial and ventricular pressure curves in two cases of severe mitral incompetence with atrial fibrillation. The x descent is abolished but the v wave is not higher than in the cases of pure mitral stenosis shown in Fig. 5. *Note.* The study was made from pressure curves superimposed by a tracing-paper technique described in the text. For the purposes of Fig. 4 to 6 the curves, taken consecutively, were superimposed photographically. This is why the electrocardiogram has a double outline.

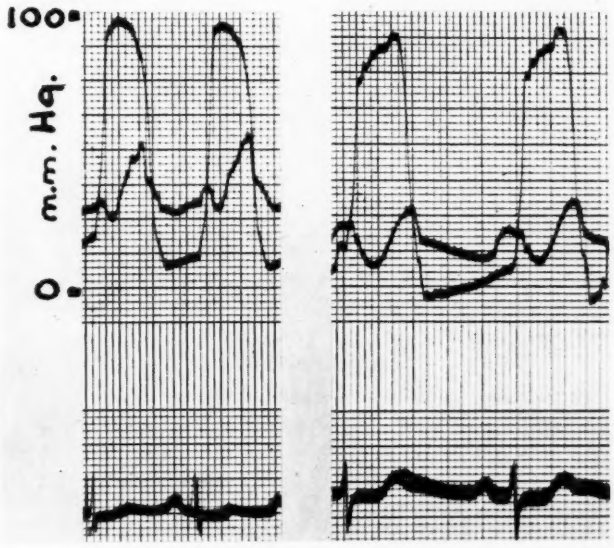


FIG. 5.—Superimposed atrial and ventricular pressure curves in two cases of mitral stenosis with sinus rhythm. The x descent reaches about as low as the pressure just before the a wave. Although the v waves are tall there is no mitral incompetence.

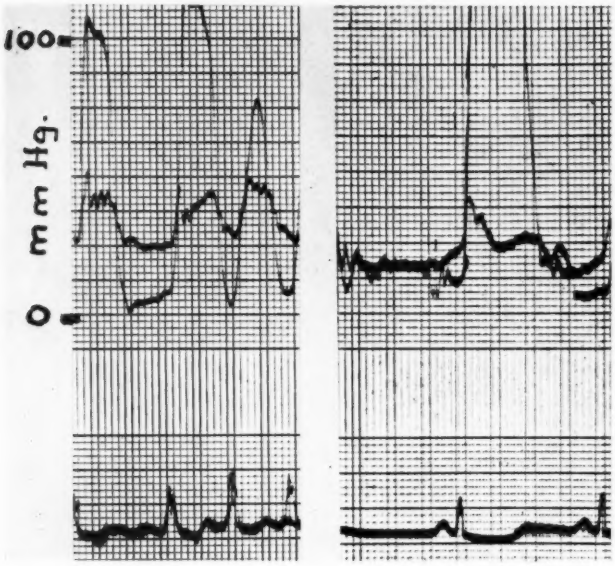


FIG. 6.—Superimposed atrial and ventricular pressure curves in two cases of mitral stenosis with no regurgitant stream. In these curves the c waves are tall and do not have the same significance as the delayed pressure rise of the curves in Fig. 4.

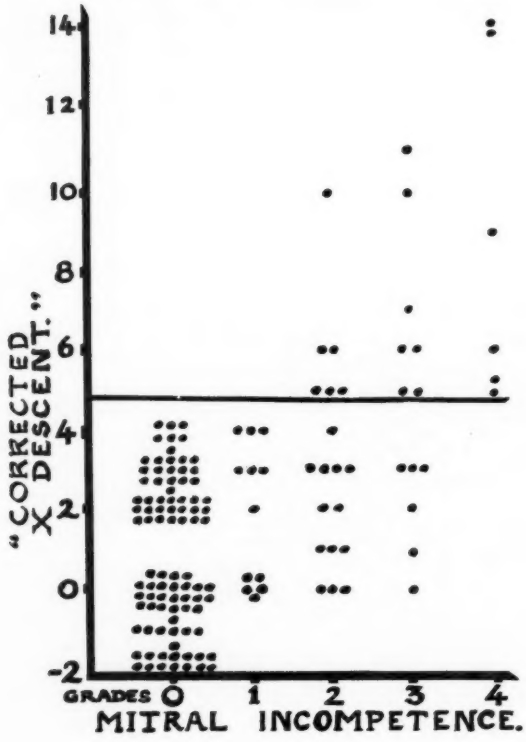


FIG. 7.—The "corrected x descent" is calculated as follows. From the x nadir are subtracted: (1) the pressure just prior to the a or c wave; (2) the number of mm. Hg of synchronous rise of atrial and ventricular pressure. When there is no x descent the atrial pressure is measured at the end of the first third of ventricular diastole. The grades of mitral incompetence are as for Fig. 1.

negative figure when the c wave was of considerable size. The results are shown in Fig. 7. An elevation above 5 mm. Hg means mitral incompetence. It was consistently present in severe incompetence and never seen when incompetence was either very slight or absent. A "corrected x descent" of less than 5 mm. Hg was sometimes present when incompetence was slight or moderate and was consistently present when it was very slight or absent.

Discussion

The height of the v wave does not indicate the presence of mitral incompetence. The present study shows that the v wave may be small in mitral incompetence and is sometimes tall in the absence of incompetence. There are many possible reasons for this. They are best explained by considering the factors concerned in the formation of the v wave. In health this wave is attributed to the filling of the atrium when the A-V valve is closed. The v wave does not reach its greatest height until the time of A-V opening and starts to fall at this time. When a tall v wave is present in mitral stenosis the peak is earlier and a considerable fall occurs before the ventricular and atrial curves cross (Fig. 5). This difference of pattern indicates that the filling of the left atrium is not the important factor in the production of a large v wave in mitral stenosis. Some workers attribute this wave to the pressure on the left atrium and pulmonary veins of the pulmonary artery and its branches. This explanation is not satisfactory because the large v wave does not diminish in ventricular extrasystoles that fail to open the pulmonary valves. It is more likely that the pressure wave is due to the contraction of the atrioventricular ring and the pressure on the large atrium of the contracting ventricles. Such a contraction would be more effective in raising the atrial pressure if the initial atrial pressure were already high, or if the ventricular contraction were increased by some factor like aortic incompetence. The degree of pressure rise must also be affected by the size and distensibility of the left atrium itself. Another factor affecting the height of the v wave is the mobility of the mitral valve cusps. Freely mobile cusps should cause the c wave to be large and unless the cusps are drawn down by the papillary muscles the pressure rise would persist until the time of A-V opening. Finally, any variation of stroke volume would affect the height of the v wave as it does in the normal heart.

The numerous factors that tend to increase the size of the v wave in mitral stenosis do not appear to make the onset of the wave any earlier. When mitral incompetence increases the height of the v wave the upstroke appears to start earlier and tends to obliterate the x descent. Thus the height of the peak of the v wave does not indicate the presence of incompetence but a rise of pressure at the time of the nadir of the x descent will indicate that incompetence is present.

There are other factors that might be important in this study. These are the left ventricular systolic pressure, the pulmonary artery pressure, the mitral valve size, and the presence of aortic valve disease. These factors have been considered and have been applied to the results without materially affecting them.

The degree of regurgitant flow has recently been estimated by a dye dilution technique (Korner and Shillingford, 1955). The disadvantage of this technique is that it does not distinguish between mitral and aortic incompetence. It would nevertheless provide a further method of establishing the value of atrial pressure curves in the diagnosis of mitral incompetence.

Summary

Left atrial and left ventricular pressure tracings were taken at operations for mitral valvotomy and compared with the degree of mitral incompetence found by the surgeon. Fifty observations were made when there was mitral incompetence, and one hundred when there was stenosis without incompetence.

Three measurements suggested by previous workers were first examined: (i) height of the v wave, (ii) v–c difference, and (iii) Ry/v ratio. None of these proved of much value in identifying the presence of mitral incompetence.

In contrast to these a new measurement has proved of value. This is termed the "corrected x descent". It consists of the pressure at the nadir of the x descent (or if this is absent the atrial pressure after the first third of ventricular systole) from which is subtracted (i) the atrial pressure just prior to the c or a wave and (ii) the extent of the c wave.

When the corrected x descent is over 5 mm. Hg there is mitral incompetence; when it is under 5 mm. Hg there is no severe incompetence, though there may be moderate incompetence.

I am grateful to Mr. O. S. Tubbs and Mr. I. M. Hill for permission to study the patients under their care and for their help in this study.

References

Biörck, G., Axén, O., Krook, H., Andrén, L., and Wulff, H. B. (1953). *Amer. Heart J.*, **45**, 13.
Björk, V. (1955). *Actor Chir. Scand.*, **107**, 466.
Bloomfield, R. A., Lauson, H. D., Cournand, A., Breed, E. S., and Richards, D. W. (1946). *J. clin. Invest.*, **25**, 639.
Bücherl, E. (1956). *Thoraxchirurgie*, **4**, 1.
Burchell, H. B., and Edwards, J. E. (1953). *Circulation*, **7**, 747.
Dexter, L., Gorlin, R., Lewis, B. M., Haynes, F. W., and Harken, D. E. (1950). *Transactions Amer. Clin. Climat. Assn.*, **62**, 1.
Eliasch, H. (1952). *Scand. J. Clin. Lab. Invest. Supp.*, **4**, 1.
Fox, I. J., Wakai, C. S., Conolly, D. C., and Wood, E. H. (1956). *Proc. Mayo Clinic*, **31**, 126.
Gérard, R., and Benyamine, R. (1956). *Arch. Mal. Cœur.*, **49**, 31.
Gorlin, R., Lewis, B. M., Haynes, F. W., and Dexter, L. (1952). *Amer. Heart J.*, **43**, 357.
Haring, O. M., Liu, C. K., and Trace, H. D. (1956). *Circulation Research*, **4**, 381.
Husfeldt, E., and Warburg, E. (1952). *Medicinske Fremskridt*, **2**, 156.
Kent, E. M., Ford, W. B., Fisher, D. L., and Childs, T. B. (1955). *Ann. Surg.*, **141**, 47.
Korner, P., and Shillingford, J. (1955). *Clin. Sci.*, **14**, 553.
Lagerlöf, H., and Werkö, L. (1949). *Scand. J. Clin. Lab. Invest.*, **1**, 147.
Logan, A., and Turner, R. (1953). *Lancet*, **1**, 1007.
McCord, M. C., and Blount, S. G. (1952). *Amer. Heart J.*, **44**, 671.
McGreggor, M., and Zion, M. M. (1955). *Acta med. Scand. Supp.*, **306**, 111.
Mackenzie, J. (1910). *Diseases of the Heart*. London. 2nd ed., p. 110.
Musser, B. G., Bougas, J., and Goldberg, H. (1956). *Amer. Heart J.*, **52**, 567.
Owen, S. G., and Wood, P. (1955). *Brit. Heart J.*, **17**, 41.
Soulié, P., Joly, F., Carlotti, J., and Sicot, J. R. (1954). *Arch. Mal. Cœur.*, **47**, 1.
Venner, A., and Holling, H. E. (1953). *Brit. Heart J.*, **15**, 205.
Wade, G., Werkö, L., Eliasch, H., Gidlund, A., and Lagerlöf, H. (1952). *Quart. J. Med., N.S.*, **21**, 361.
Wiggers, C. J. (1923). *Circulation in Health and Disease*. London, p. 533.
——, and Feil, H. (1922). *Heart*, **9**, 149.
Wynn, A., Matthews, M. B., and McMillan, I. K. R. (1952). *Lancet*, **2**, 216.

CLINICAL AND RADIOLOGICAL ASPECTS OF CALCIFICATION OF THE MITRAL REGION

BY

EINO LINKO AND ERKKI SYSIMETSÄ

From the Medical Clinic and the Cardio-Respiratory Research Unit, University of Turku, Finland

Received September 20, 1957

Calcification of the cardiac valves and adjacent tissues has long been known to both clinicians and pathologists. Previous rheumatic endocarditis has been considered the cause of the calcification, and this is of clinical importance. The incidence of calcification associated with rheumatic valvular disease has been examined on the basis of autopsy findings by Epstein (1940) among others; he found calcification that varied in size from microscopically small particles to large calcareous masses in 64 out of 148 cases. This calcification not only involves the cardiac valve leaflets, but may also appear in the annulus fibrosus, the wall of the left atrium, and the papillary muscles. Similar calcification may develop without previous rheumatic infection, especially after middle age. Simon and Liu (1954) found calcification of the mitral valve annulus in 10 per cent of 590 unselected, consecutive autopsies and, like some others, observed that the incidence increased with age.

The occurrence of calcification within the heart at X-ray examination was noted fairly early. Thus, for instance, Klason (1921) described a case of partial calcification of the mitral ring observed by fluoroscopy. Saul (1932) was apparently the first to publish X-ray pictures of three cases of this kind. Subsequently isolated cases or small series have been reported (e.g. Sossman and Wosika, 1933; Bishop and Roessler, 1934; Baumann, 1936; and Sundberg, 1941).

Most investigators consider radioscopy more trustworthy than radiography for the detection of intracardial calcifications. This is natural since calcification that is frequently present in the lungs, hila, or rib cartilages produces shadows in the region of the heart valves and cannot be readily distinguished from calcification of the valves. In radioscopy, however, the valvular calcification differs in mobility from the extra-cardiac calcification since the former moves with the cardiac rhythm and the latter with respiration. However, the subjectiveness and other secondary factors often reduce the reliability of radioscopic observation.

The progress made in recent years in heart surgery has reawakened interest in the problem of the calcification of mitral valves and of the annulus fibrosus. Mitral valve calcification is frequently encountered in connection with cardiac operations, according to Bailey and Morse (1957) with an incidence of 42 per cent. Opinions about the significance of mitral valve calcification as a contra-indication to surgery and as a factor influencing the results of mitral valvotomy seem, however, to be divergent.

Since it is the duty of a physician not only to make a clinical diagnosis of valvular disease but also to express an opinion about any contra-indications, numerous investigators have stressed the importance of a thorough radiological examination of the heart, particularly to detect calcification. Radioscopy has been used generally in such examinations and it has its strong points, but sometimes calcification can be recognized also in ordinary films. These have been used, for instance, by Wynn (1953) in an extensive study of the incidence of calcification in mitral valvular disease of various clinical types.

In recent years tomography has gained more and more favour alongside the above methods of investigation. Hohenner (1940) was apparently the first to present a tomogram showing a partially calcified mitral ring. The superiority of tomography has been particularly stressed by Soloff *et al.* (1954, 1955) since with its aid it is possible to determine more reliably the extent of the calcification: in their 16 patients with mitral stenosis, they found valvular calcification in twelve.

The aim of the present study was to examine by means of simultaneous tomography the region of the mitral valve in patients with clinically proved mitral disease and to correlate the findings with clinical observations for the evaluation of indications for surgery.

Material and Methods

The series comprised 68 consecutive unselected patients with rheumatic mitral and/or aortic valvular disease of varying degree of clinical severity who were being treated or examined at the University Medical Clinic in Turku.

FIG. 1.—Tomography in right oblique projection shows a pronounced calcified area about 1 × 2 cm. in the region of the mitral valve, about 4 cm. ventral to the left posterior wall of the heart. A man, aged 53 years. Slight dyspnœa in 1944, and more severe in 1945. Treated in hospital with diagnosis of mitral regurgitation and atrial fibrillation.

FIG. 2.—Tomography in slight right oblique projection reveals partial calcification of the mitral annulus about 3·5 cm. in diameter, 4 cm. ventral to the left posterior wall of the heart. A woman, aged 33 years. Polyarthritis about ten years previously. Irregular heart action on exertion during the last eighteen months, and dyspnœa during the past six months. No treatment before admission to hospital with a diagnosis of mitral stenosis.

The routine cardiological examination consisted in most cases of a phonocardiographic confirmation of the auscultation findings, a 12-lead electrocardiogram, a thorough radiological examination of the heart in which particular attention was paid to the relative magnitudes of the left atrium and left ventricle, and a measurement of the cardiac volume.

Tomography. The tomograms were recorded in a slightly right anterior oblique projection (about 20 degrees). When this projection is used the various cardiac valves are not superimposed to the same extent as when the angle is 40 degrees and can be more easily distinguished from each other, and furthermore the shadow of the spine is not projected on the shadows of the valves as in tomograms taken in the posterior-anterior direction. Also the thickness of the object is not magnified to the same extent as in a tomogram taken in the normal oblique direction. The shadows of the valves could be differentiated best in a tomogram taken in the left oblique projection, but the angle must then be at least 45 degrees before the shadow of the spine can be eliminated, and then the thickness of the heart and the object will reduce the contrast so much that we have found it preferable to use an angle of 20 degrees as mentioned above.

The recordings were made with a Siemens Universal tomograph with the patient in the standing position, with the following exposure data: 250 mA (2·5 seconds), 80–100 kV, distance 150 cm. The tomograms were taken with a Siemens simultaneous cassette (7 exposures at 1-cm. distances). The good features of this cassette were shown well in this type of recording: the adjustment is easily made and a series of exposures are obtained from a region 7 cm. thick and consequently the amount of radiation the patient is exposed to is considerably smaller than when single tomograms are taken. There is also the advantage that the examination does not tire the patient excessively and requires less time.

Results

For the sake of brevity, the extent and intensity of the calcifications are graded as follows.

Slight (+)	..	Small, diffuse calcified areas in the valves.
Moderate (++)	..	Clearly discernible calcification in the valve leaflets seen at different planes.
Severe (+++)	..	Extensive calcification of the mitral valve and annulus fibrosus either with or without calcification of the aortic valves.

The tomograms of 24 of the 68 patients examined revealed calcification which varied in severity as follows: slight in 6, moderate in 10, and severe in 8 cases. In only one of these patients was the existence of calcification established with certainty by ordinary X-ray examination.

Correlation with Clinical Findings

By examining the past histories of the patients, the time since the onset of the rheumatic infection that caused the valvular disease could be determined with a high degree of certainty in 50 patients (Table I). It was observed that no calcification had developed if this time was less than ten years. When the time was longer, no clear differences were noted between time groups although calcification was observed in 5 of 6 patients where the time was over 30 years. In these cases factors associated with their age, apart from the time since their rheumatic endocarditis, may have exerted an effect. No correlation was established between the extent of the calcification and the length of time since the infection.

As regards the correlation between the age of a patient and the incidence of calcification, none of the patients under 30 had any calcification and the older age groups showed no difference in incidence (Table II).

On the basis of the clinical findings and special investigations, the material could be divided into groups as shown in Table III. The greatest relative incidence of calcification of the mitral area occurred in the group in which the stenosis was dominant and the incidence was much less in those where the regurgitation was dominant. The other groups are too small to permit any conclusions.

A closer examination of the group of 21 cases of mitral stenosis revealed that in 11 the clinical status and other findings pointed to the advisability of surgery (auricular fibrillation and age of the patient have been considered only relative contraindications): in four of these eleven the mitral valve

TABLE I

INCIDENCE OF CALCIFICATION ACCORDING TO TIME FROM ONSET OF RHEUMATIC INFECTION

Years	10 or less	11–20	21–30	31 or more
Patients with calcification ..	0	7	5	5
Patients with no calcification	16	11	5	1

TABLE II

INFLUENCE OF AGE ON THE PRESENCE OF CALCIFICATION

Age in years	30 or less	31–40	41 or more
Number with calcification ..	0	9	15
Number with no calcification	19	10	15

TABLE III

INFLUENCE OF THE VALVE LESION ON THE PRESENCE OF CALCIFICATION

Main valve lesion	Number of patients	Number with calcification
Stenosis dominant	21	11*
Regurgitation dominant	26	6
Stenosis and regurgitation	8	3
Mitral and aortic valve disease	13	4

* In one case pulmonary stenosis of the valvular type was also established by right heart catheterization

and/or the annulus fibrosus were detectably calcified. Of the remaining 10 the reduction in functional capacity was so slight (Class I) in two that immediate surgery was not indicated and no calcification was evident. Four further patients belonged to Classes II and III, but other diseases contra-indicated surgery; three of these had calcification. The remaining four belonged to Class IV with absolute contra-indications to surgical intervention: all these showed calcification of higher order (+++).

DISCUSSION

It is of interest that increasing attention has been paid recently to mitral calcification from the surgical angle also. This may be due to the fact that the range of indications has been continuously extended as far as age is concerned, but it should also be remembered that calcification in the mitral area is not unusual even in young persons (e.g. Wynn, 1953). In children calcification is extremely rare, although severe stenosis may occur (Nadas, 1957).

The effect of calcification on the function of the mitral valve has been discussed, and, for instance, Wynn (1953) concluded that gross calcification of the mitral valve has no striking connotations in either a clinical or hæmodynamic sense, except in relation to mitral regurgitation. Simon and Liu (1954) thought that although mitral calcification might be of rheumatic origin, it closely resembles atherosclerotic changes in many respects and further that it may occur as a separate process without the valve itself being involved. However, sclerosis of a tissue that is normally very mobile must in some way influence the hæmodynamics, particularly as autopsy examinations show that calcification, although it may not be visible, may involve the chordæ tendineæ, papillary muscles, and even larger areas (Epstein, 1940).

Very divergent opinions have been presented recently on the role of mitral calcification in deciding about surgical treatment. Chavez *et al.* (1955), for instance, have considered calcification of the mitral valve one of the pitfalls of mitral valvotomy. The opinion of Black and Harken (1957) is that although mitral calcification has previously been considered a relative contra-indication, its possible dangerous effects have been greatly reduced by recent developments in surgical techniques: furthermore, as a paradoxical finding, they mention that some of the best results have been achieved in patients with mitral calcification. However, Bailey and Morse (1957) have come to the conclusion that great caution should be exercised whenever calcification is noted. The same conclusion, or perhaps an even more pessimistic view about the influence of calcification, was reached by Winsor (1956) from his study of a series of 645 operations for mitral stenosis. In those patients with calcification the mortality of the operation was over ten times that in other patients of his series, and the rate of unsuccessful valvotomy was about 50 per cent.

The present series leads one only to agree that it is necessary to make as accurate an analysis as possible of mitral calcifications when considering surgery for such patients. This statement applies not only to operations for mitral stenosis, since quite recently a method had been considered for the operative correction of mitral regurgitation (Glover and Davila, 1957). In addition, one must always take into account that typical mitral disease may be accompanied by rheumatic lesions of the aortic valves, which may also include calcification and can be determined only with difficulty by clinical or special methods.

Tomography may also reveal features of other valves that may be of decisive importance when considering the feasibility of surgery. As a practical conclusion from the results of the present study the authors believe that tomograms of each plane of the heart should be recorded in all cases where there are indications for surgery.

Simultaneous tomography is a fairly easy and reliable method compared with radioscopy, which in itself furnishes an instructive dynamic picture but is liable to the shortcomings of subjective methods. In tomograms the shadows of calcification outside the heart are eliminated, and it is relatively easy to determine the site of the valvular calcification from the depth of the image plane. The edges of the calcification are blurred in the tomogram owing to the movement of the valves during the long exposure, but the shadows nevertheless stand out in sharp contrast against the otherwise uniform shadow of the heart, and hence the possibility of erroneous interpretation is slight.

Summary

Tomographic studies have been conducted using a Siemens Universal tomograph on 68 unselected, consecutive patients with rheumatic valvular heart disease. Calcification of the valve or annulus fibrosus of varying degrees was detected in 24 of them. Two typical cases are described in detail.

The occurrence of calcification did not depend on the age of the patient, except that it was not observed in patients under 30 years. Neither did the incidence of calcification depend clearly on the time that had elapsed since the onset of the rheumatic infection that had caused the valvular damage. Neither the severity nor the extent of the calcification could be correlated with these time factors.

Calcification was relatively more frequent in patients with mitral stenosis, and was most extensive in the mitral leaflets and the annulus fibrosus.

The authors believe that in all patients with mitral disease in whom surgery is contemplated, a complete tomographic examination of the whole heart is necessary before a reliable pre-operative evaluation can be made.

References

Bailey, C. P., and Morse, D. P. (1957). *J. thorac. Surg.*, **33**, 427.
Baumann, W. (1936). *Münch. med. Wschr.* 1114, quoted by Milatz (1956).
Bishop, P. A., and Roessler, H. (1934). *Amer. J. Roentgenol.*, **31**, 1.
Black, H., and Harken, D. E. (1957). *Amer. Heart J.*, **53**, 439.

Chavez, I., Vaquero, M., and Mendoza, E. (1955). *Acta cardiol.*, **10**, 209.
Epstein, B. S. (1940). *Arch. intern. Med.*, **65**, 279.
Glover, R. P., and Davila, J. C. (1957). *Circulation*, **15**, 661.
Hohenner, K. (1940). *Fortschr. Geb. Röntgenstr.*, **61**, 16.
Klason, M. L. (1921). *Acta radiol. (Stockh.)*, **1**, 162.
Milatz, W. (1956). *Fortschr. Geb. Röntgenstr.*, **85**, 282.
Nadas, A. S. (1957). *Pediatric Cardiology*. W. B. Saunders Co., Philadelphia and London.
Saul, W. (1932). *Fortschr. Geb. Röntgenstr.*, **46**, 450.
Simon, M. A., and Liu, S. F. (1954). *Amer. Heart J.*, **48**, 497.
Soloff, L. A., Zatuchni, J., and Fisher, H. (1954). *Circulation*, **9**, 367.
—— (1955). *Arch. intern. Med.*, **95**, 219.
Sossman, M. C., and Wosika, P. H. (1933). *Amer. J. Roentgenol.*, **30**, 328.
Sundberg, C. G. (1941). *Acta radiol. (Stockh.)*, **22**, 834.
Winsor, H. M. (1956). *Austral. N. Zealand J. Surg.*, **25**, 248.
Wynn, A. (1953). *Brit. Heart J.*, **15**, 214.

ATRIAL DISSOCIATION

BY

MARIO GOMES MARQUES

From The Civil Hospitals of Lisbon

Received September 30, 1957

Schrumpf (1920) was the first to describe a clinical electrocardiogram assumed to represent atrial dissociation. He figured a curve apparently normal with a series of rhythmic and independent deflections resembling auricular waves superadded to it. In his case these independent deflections were ineffective to evoke ventricular responses, their rate was not rapid, and they fell in varying time-relation with the waves of the fundamental rhythm which they failed to affect.

Since then a number of electrocardiograms showing essentially the same events have been published by Bay and Adams (1932), Géraudel (1935), Duclos (1935), Lian and Golblin (1938), Dominguez and Bizzozero (1937), Giraud *et al.* (1943), and Deitz *et al.* (1957).

The superadded summits have been labelled P', P'', P^2, and p, in order to denote their auricular nature and to separate them from the apparently normal conducted atrial waves which are seen in the same records. Such cases have been related with another type of pararrhythmia, assumed to depend upon the same mechanism of atrial dissociation, in which two independent, grossly abnormal auricular rhythms (auricular fibrillation plus auricular flutter), or a distinctly anomalous activity with a simple auricular rhythm co-exist.

Most authors have assumed that a completely independent activity of each atrium afforded a plausible explanation of these electrocardiograms, or, in other words, that an interauricular dissociation would be present in each example of this condition.

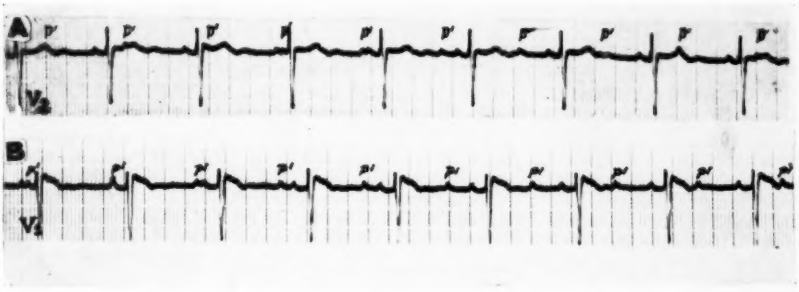


FIG. 1.—Two cases in which a series of rhythmic and independent deflections, probably auricular in origin, is seen superadded to the apparently normal dominant rhythms. Record *A* is lead V2 obtained in Case 1: *B* is lead V1 obtained in Case 2. These curves illustrate the complete independence between the atrial waves conducted to the ventricles and those of the superadded rhythm. (Standardization: 1 cm.=1 mV; time interval: 0·2 sec. between heavy vertical lines.)

These conventional views harmonize with evidence presented by Condorelli (1929) and others that examples of interauricular dissociation occur in animal experiments. However, experimental precedent does not imply that electrocardiograms showing two unrelated series of waves, apparently auricular in origin, always represent a state of complete independence between the atria.

The purposes of this paper are to report two cases of this rare electrocardiographic abnormality and to discuss the concept of atrial dissociation.

Case Reports

Case 1. A woman of 76, was first seen with ten months' history of breathlessness and moderate swelling of the lower limbs. At that time she was digitalized with lanatoside C and was asymptomatic.

On examination she had very slight œdema of the ankles. There was no dyspnœa nor crepitations at the lung bases, and the liver was not enlarged. The heart sounds were normal, no murmurs were heard, the pulse was regular, and the blood pressure was 180/80 mm. Hg. Screening revealed a slightly enlarged left ventricle. At that time a cardiogram (Fig. 2) showed regular rhythm, apparently sinus in origin, at a rate of 71, in leads I and II. This rhythm was replaced in the other leads by another rhythm, probably a supranodal or "upper" nodal rhythm (rate 65). In leads V1, V3, and V6 a secondary set of atrial waves (rate 86), independent of the dominant rhythm and not conducted to the ventricles, was present.

Seven days later another electrocardiogram (Fig. 3) showed regular rhythm, probably sinus in origin (rate 68) in all leads, and a secondary set of atrial waves (rate 77) in leads V1, V2, and V3. Several subsequent records have failed to reveal the distinctive pattern of atrial dissociation or abnormal pacemakers.

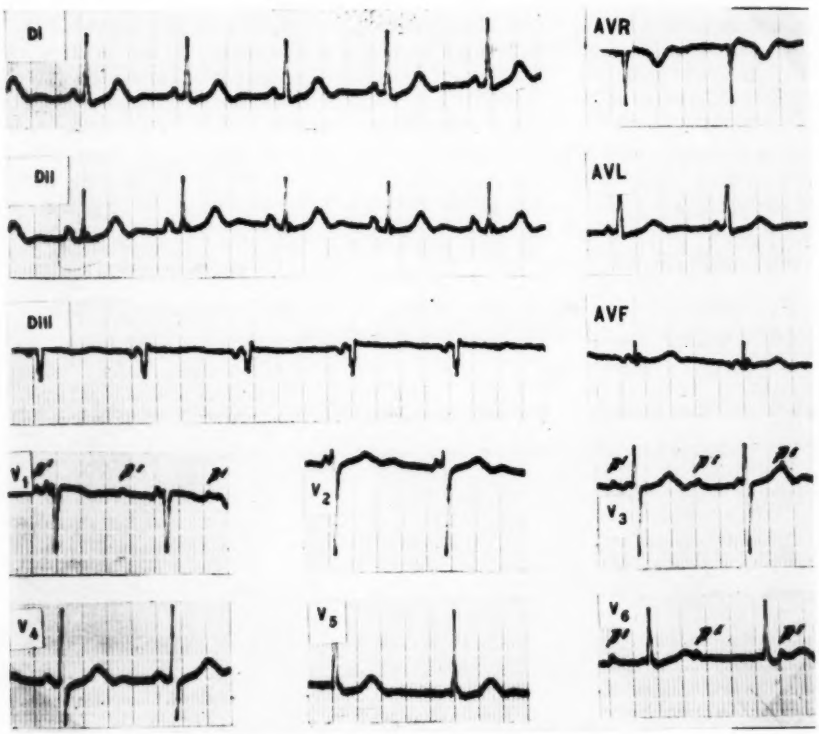


FIG. 2.—First electrocardiogram obtained in Case 1. The apparently sinus rhythm recorded in leads I and II changed in lead III and unipolar leads to a probably supranodal or upper nodal rhythm. In leads V1, V3, and V6 a secondary set of atrial waves not conducted to the ventricles and completely independent from those of the fundamental rhythm is seen.

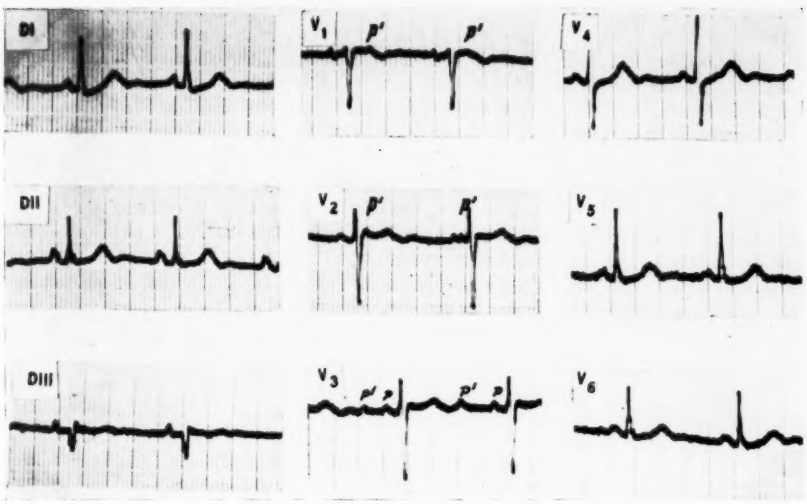


FIG. 3.—Second electrocardiogram obtained in Case 1. The fundamental rhythm is apparently sinus in origin in all leads. The superadded atrial waves are evident in leads V1, V2, and V3.

Case 2. A man of 57, was admitted complaining of severe dyspnœa and œdema. On first examination he was orthopnœic and cyanosed. The pulse was regular and the blood pressure 130/80 mm. There were a raised jugular venous pressure, crepitations at the lung bases, and evidence of severe bronchitis and emphysema. The heart sounds were normal and there were no murmurs. The liver was enlarged and there were massive œdema of the lower limbs and sacral œdema.

Roentgen examination of the chest revealed a slightly enlarged left ventricle, a convex cardiovascular angle at the left border and a calcified aortic arch. An electrocardiogram showed a regular sinus rhythm and minor evidence of left ventricular strain.

Treatment consisting of oxygen, digitalization with lanatoside C, acetazolamide and mercurial diuretics, antibiotics, and a low-salt diet resulted in prompt improvement. Relief of the dyspnœa, disappearance of the crepitations at the bases of the lungs and of œdema were obtained in one week. At that time a second record (Fig. 4—I) showed a regular rhythm, apparently sinus in origin, at a rate of 64. A secondary set of atrial waves, independent of the dominant rhythm and not conducted to the ventricles, was present in leads V1, V2, V3, and V5 (rates of 54 to 66). A third record (Fig. 4—II) eight hours later showed the same secondary activity in leads V1, V2, and V6 (rates of 56 to 83). At that time an œsophageal electrocardiogram at various levels failed to reveal the superadded atrial activity, a point that suggests it was right atrial in origin, since immediately before and after it was portrayed in præcordial leads, particularly in those recorded from the right chest. Twenty-four hours later the super added waves were present (Fig. 4—III) in leads V1, V5, and V6 (rates of 71 to 77).

Several subsequent records, including an intracardiac electrocardiogram at various right atrial levels failed to reveal the existence of atrial dissociation.

DISCUSSION

Close inspection of many published electrocardiograms claimed to demonstrate two simultaneous and independent atrial activities does not permit acceptance of the evidence as conclusive. Thus, extraneous somatic waves in cases with sinus rhythm, technical artifacts, and other sources of error or a misconception of the nature of the large auricular waves in right chest leads in patients exhibiting typical fibrillation waves in left chest and limb leads, are frequently misinterpreted in early papers on the subject and described as electrocardiographic evidence of atrial dissociation.

However a few published electrocardiograms are convincing like those showing two independent sets of atrial waves, the tracings published by Lombardini and Aviles (1939) and Bellet (1953) as

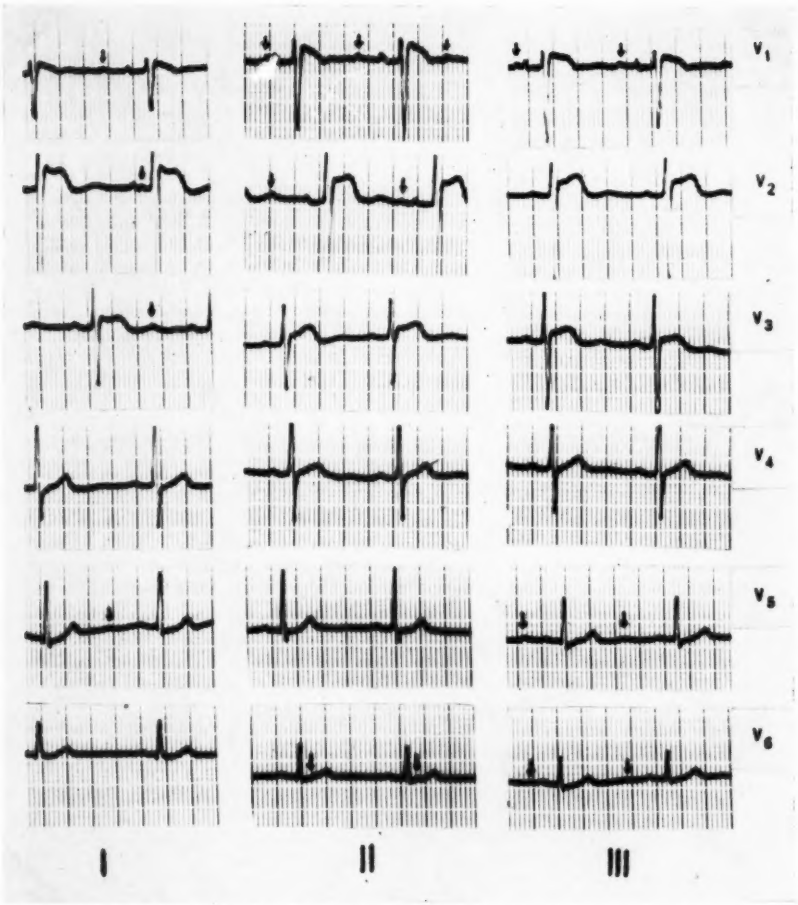


FIG. 4.—Unipolar chest leads taken at different times in Case 2. The three records demonstrate the variability of the rate of the superadded rhythm from lead to lead in the same record.

examples of simple atrial activity with superimposed atrial flutter, the tracing published by Mussafia and Jacovella (1957) as a case of simple activity (probably sinus rhythm) with simultaneous paroxysmal atrial flutter and those published by Araújo Moreira (1951) where the fundamental mechanism is that of auricular fibrillation while a simple, not rapid, atrial rhythm is evident in præcordial leads.

Two further cases were recently described by Deitz *et al.* (1957). They are remarkable, since they provide an illustration of transitional stages between simple dissociation, where two independent series of slow atrial waves co-exist, and more complex pararrhythmias in which the superadded rhythm is auricular flutter or auricular fibrillation.

In all these cases the cardiac nature of the superadded electrical activity seems probable and its atrial origin is supported by the contour of the oscillations. These are best recorded by placing the exploring electrode over the right chest, sternum, or at various œsophageal levels. This seems to be another point that suggest an atrial origin for the superadded waves.

A review of the associated disturbances of rhythm in cases with atrial dissociation indicates that

a variety of arrhythmias is observed in this curious electrocardiographic phenomenon. Ectopic premature systoles are seen to occur as in any other condition, and may be nodal or ventricular in origin. Supranodal or "upper" nodal rhythm and second degree A-V block are also seen to occur. In general the dominant rhythm has the usual average rate for each particular case. In those cases showing two independent simple rhythms the auricular rates of the dominant rhythm are sometimes faster and sometimes slower than that of the auricular superadded deflections.

Superimposed auricular activities are better displayed in different leads in different patients, the contour of the atrial waves varies from patient to patient, and in several cases these waves are not portrayed in the limb leads. In our cases the leads where the specific pattern of atrial dissociation is identified change from one record to the next. This pre-supposes, if a true interauricular dissociation is assumed, a change of direction of the spread of the excitation. It may be said that the disparity in the electrocardiographic findings in atrial dissociation is caused by the position of the heart in the chest, by the site of the ectopic pacemakers, and by the manner in which the excitation waves are distributed to the auricular syncytium. This does not explain why and how the ectopic impulse could spread over the whole surface of an atrium without being recorded in the limb leads, even when the spread of the excitation wave changes its direction from time to time.

From these considerations it seems unwise to accept the interauricular dissociation as an adequate explanation for all cases under discussion. It is of interest to remember that Lewis (1925) discarded the hypothesis of an interauricular dissociation as an explanation for the Schrumpf's case. However, a few years later Condorelli (1929) found that he could induce an interauricular dissociation in dogs by ligating the interatrial branch of the left coronary vessel. By this method he found that dissociation of the two atria develops with sinus rhythm in the right atrium and fibrillation in the left atrium. Condorelli also found an interatrial dissociation with sinus rhythm in the right atrium and left atrial arrest by ligating in a dog the anterior descending branch of the left coronary artery proximal to the origin of the interauricular branch which sometimes arises from that vessel. Dissociation of the two atria has been supported by the investigations of Scherf and Siedek (1934). A unique convincing direct observation of this phenomenon in human beings has been reported by Marcel and Exchaquet (1938). Their studies on the electrocardiographic patterns of human fœtus without possibility of survival were carried out with open chest, and, this way, they were able to correlate the electrical and mechanical events of the cardiac cycle. Analysis of their electrocardiograms strongly suggests that atrial dissociation occurs in human beings. However, the applicability to clinical conditions of results obtained in such work is doubtful and it seems, at the present stage, that dissociation of the two auricles in human beings cannot be considered as established. None of the observations made in connexion with human cases of double atrial activity includes any other evidence beside the electrocardiographic tracings. On the other hand, it is not possible to find any observations that could not be understood as the result of the spread of impulses over circumscribed areas of the atria.

In view of such reasons the use of the term "interauricular dissociation" for this kind of pararrhythmia does not seem justified and it would seem better, from a clinical point of view, to use the wider terms "atrial dissociation" or "intraauricular dissociation." The observations of Lewis (1925), Prinzmetal *et al.* (1952), Puech (1954), and Abildskov *et al.* (1955) led them to conclude that the excitation wave spreads through the atria in a uniform radial fashion.

If a zone of refractory tissue has to be invoked in cases of atrial dissociation, those who accept an independent activity of each atrium as an explanation to these cases have to conceive a block zone running along the line of junction of the two atria. This, however, seems highly improbable. It is possible that different mechanisms are responsible for atrial dissociation, while occasionally it may be due to an interauricular block. A plausible explanation of many cases could be afforded by assuming that they are due to the simultaneous activities of two or more centres producing impulses that yield independent excitation processes of different parts of the atrial myocardium, with a dynamic bidirectional block along their boundaries.

For the purposes of this paper the term "dynamic bidirectional block" would be understood

as meaning a block guarding each centre against interference by the other centres, protecting these against the impulses of the first, and, moreover, at times changing its spatial localization in the atrial myocardium. This hypothesis presupposes that the area responding to each centre varies from time to time and, theoretically, it could be at different times, greater or less than a whole atrium. A similar mechanism was postulated by Moreira (1951) as an explanation of a repetitive paroxysmal tachycadia of certain cases.

These views have received support from experimental work eliciting dissociation of small areas of atrial muscle and particularly from the extensive clinical studies on intracardiac potentials of Giraud *et al.* (1955). These authors found, in cases with auricular fibrillation, several independent areas where the activity is rhythmic and coordinated, surrounding rhythmic foci of impulse formation. These areas are separated by wandering boundaries from the remainder of the atria, where the disorganized activity, typical of fibrillation, is present. Giraud *et al.* thus showed that two, or more, pararrhythmic centres mutually protected against each other's impulses by dynamic bidirectional blocks may be present in human atria.

It is concluded that electrocardiograms showing two simultaneous and independent atrial activities do not necessarily mean the existence of an interatrial dissociation and, commonly, the block zone assumed to be present in these cases changes its spatial localization from time to time, with a simultaneous change of the areas responding to each centre; and that atrial dissociation while rare in the classical variety (type Schrumpf) is probably, in complex forms, widely present in human beings.

Summary

Two more cases with atrial dissociation (type Schrumpf) are reported. Previous clinical examples and experimental evidence of atrial dissociation are briefly discussed. Reasons are given for the assumptions that this phenomenon cannot always be considered as being due to an interatrial dissociation, that commonly the block zone between the independent atrial areas must be wandering, and that the complex forms of this pararrhythmia probably are much more common than has been widely accepted until recently.

References

Abildskov, J. A., Cronvich, J. A., and Burch, G. E. (1955). *Circulation*, **11**, 97.
Bachmann, G. (1916). *Amer. J. Physiol.*, **41**, 309.
Bay, E. B., and Adams, W. (1932). *Amer. Heart J.*, **7**, 759.
Bellet, S. (1953). *Clinical Disorders of the Heart Beat*. Lea & Febiger, Philadelphia.
Castro, O. de (1934). *Arch. Mal. Cœur*, **27**, 282.
Condorelli, L. (1929). *Ztschr. ges. exper. Med.*, **68**, 516.
Dagnini, G. (1937). *Cuore e Circol.*, **21**, 571.
Deitz, G. W., Marriott, H. J. L., Fletcher, E., and Bellet, S. (1957). *Circulation*, **15**, 883.
Dominguez, C., and Bizzozero, R. C. (1937). *Arch. Mal. Cœur*, **28**, 121.
Duclos, F. (1935). *Arch. Cardiol. Hemat.*, **16**, 175.
Erfmann, W. (1913). *Ztschr. f. Biol.*, **61**, 155.
Eyster, J. A. E., and Meek, W. J. (1916). *Artch. intern. Med.*, **18**, 775.
Ferreira, O. (1935). *Presse méd.*, **43**, 260.
Géraudel, E. (1935). *Arch. Mal. Cœur.*, **28**, 121.
Giraud, G., Latour, H., and Puech, P. (1955). *Ann. Lab. Cardiol. Clin. Méd.*, 47.
Giraud, P., Jouve, A., and Senez, J. (1943). *Arch. Mal. Cœur*, **36**, 21.
Lewis, T. (1925). *The Mechanism and Graphic Registration of the Heart Beat*. 3d. ed., Shaw and Sons, London.
Lian, C., and Golblin, V. (1938). *Arch. Mal. Cœur*, **31**, 52.
Lombardini, R. V., and Aviles, M. D. (1939). *Rev. Argent. Cardiol.*, **5**, 380.
Marcel, M. P., and Exchaquet, J. P. (1938). *Arch. Mal. Cœur*, **31**, 504.
Moreira, J. A. (1951). *Clin. contemp.*, **5**, 328.
Mussafia, A., and Jacovella, G. (1957). *Cardiologia*, **31**, 173.
Prinzmetal, M., Corday, E., Brill, I. C., Oblath, R. W., and Kruger, H. E. (1952). *The Auricular Arrhythmias*. Charles C. Thomas, Springfield, Ill.
Puech, P. (1956). *L'activité électrique auriculaire normale et pathologique*. Masson et Cie., Paris.
Scherf, D., and Siedek, H. (1934). *Ztschr. klin. Med.*, **127**, 77.
Schrumpf, P. (1920). *Arch. Mal. Cœur*, **13**, 168.
Thörel, C. (1910). *Verhandl. deutsch. pathol. Gesellsch.*, **14**, 71.

DIRECT LEFT ATRIAL PRESSURE TRACINGS AND THE DEGREE OF MITRAL OBSTRUCTION

BY

STANLEY R. McCAMPBELL

From the Postgraduate Medical School and the Department of Medicine, Hammersmith Hospital

Received August 8, 1957

Attempts have been made to assess the degree of mitral obstruction in mitral stenosis by analysing the diastolic part of indirect left atrial pressure tracings (Owen and Wood, 1955). These pressure tracings have been obtained using a cardiac catheter in the pulmonary artery in the "wedge" position, and available evidence suggests that direct left atrial pressure tracings are comparable to indirect tracings in this measurement (Connolly *et al.*, 1953; Owen and Wood, 1955; Dickens *et al.*, 1957). Owen and Wood (1955) state that the behaviour of the *y* descent (or *Ry/v**) provides evidence of the presence or absence of obstruction at the mitral orifice, a slow *y* descent suggesting obstruction, and a sharp *y* descent absence of obstruction. The present study is an attempt to analyse *Ry/v* in cases of surgically proven mitral stenosis before and after mitral valvotomy.

Material and Methods

Left atrial pressure tracings were made at the time of mitral valvotomy with the chest and pericardium open, through a 19 gauge needle on the end of a #8 U.S. saline-filled catheter. The manometers used were of the conductance type and set with zero pressure referred to the sternal angle. D.C. amplifiers and mirror galvanometers were used. Records were made photographically before and after mitral valvotomy, and *Ry/v* calculated for each case by the method described by Owen and Wood (1955).

The patients represent a consecutive series of mitral valvotomies performed during the last three years at Hammersmith Hospital under the direction of Mr. W. P. Cleland. The estimation of mitral valve size and the presence or absence of mitral regurgitation were noted by the surgeon at the time of operation in each case. The patients are divided for purposes of discussion into two groups: (i) those without mitral regurgitation, and (ii) those with slight or moderate mitral regurgitation.

Results

Fig. 1 shows a graph of *Ry/v* and its relationship to mitral valve size; it relates to 75 measurements in 48 patients without mitral regurgitation. Forty-eight of the measurements were made before valvotomy and 27 measurements following valvotomy. The correlation coefficient is +0·255, which is significant (0·05>P>0·01). It is, however, unimportant, since only 6·5 per cent of the variation in *Ry/v* can be accounted for by variation in valve size. Thus, if *Ry/v*=0·5, the valve size predicted from these figures could range from −0·38 to 3·10 cm.^{2}.

* *Ry/v* is the rate of descent of the *y* wave related to the filling pressure, *v*. $Ry/v = \frac{(P1-P2)\text{ mm.}}{P1\text{ mm.} \times (T2-T1)\text{ sec.}}$

Where P1 = Pressure at peak of *v* wave.
P2 = Pressure at the end of the fall of *y* wave.
T2 = Time at the end of the fall of *y* wave.
T1 = Time at the peak of *v* wave.

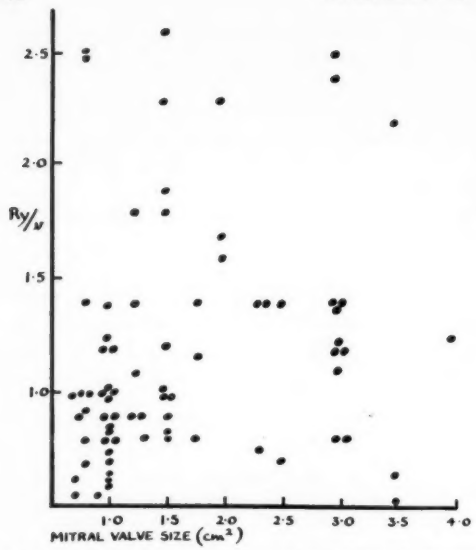


FIG. 1.—Relationship of *Ry/v* to mitral valve size in a group of patients without mitral regurgitation.

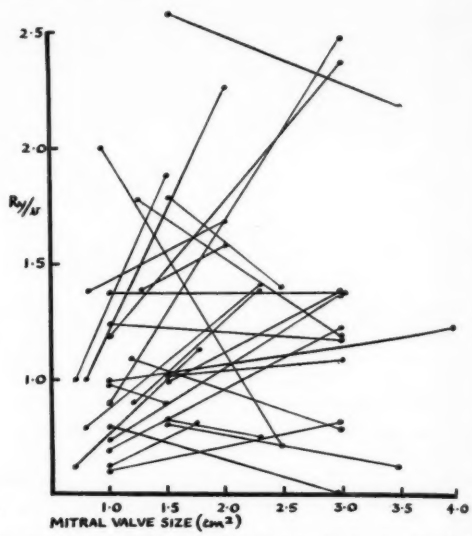


FIG. 2.—Relationship of *Ry/v* to mitral valve size before and after mitral valvotomy in the absence of mitral regurgitation.

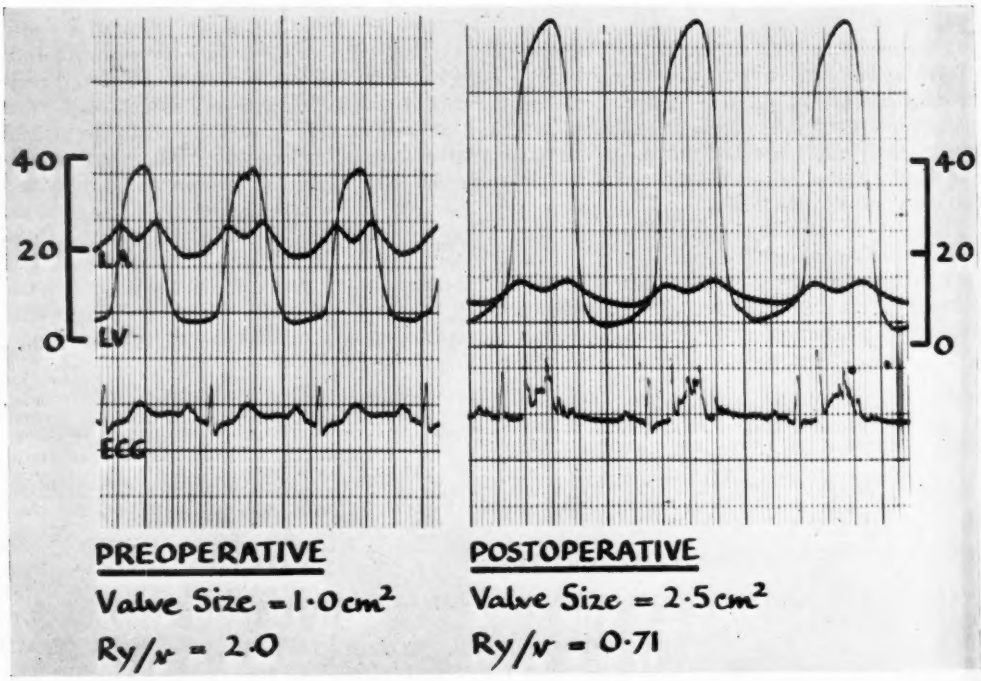


FIG. 3.—Left atrial and left ventricular pressure tracings in a case of tight mitral stenosis before and after mitral valvotomy. Note the change in heart rate. Simultaneous left ventricular pressure tracings are recorded here on a different scale.

It may be seen from the graph that given a figure for Ry/v of 2·5, the mitral valve size in this series ranged from 0·8 to 3·0 cm.^{2}. With a mitral valve size of 0·8 cm.^{2} the Ry/v ranged from 0·7 to 2·5. Similarly, with a valve size of 3·5 cm.^{2}, Ry/v ranged from 0·5 to 2·2. It is true that in the group whose valve measured less than 1·5 cm.^{2}, Ry/v was less than 1·5 in 86 per cent, but in the group with valve size over 2·5 cm.^{2} (and thus no hæmodynamically significant stenosis), 79 per cent had Ry/v figures of less than 1·5. It is difficult to see how these values would be worthwhile in estimating the degree of mitral stenosis in a single case.

If Ry/v were a measure of mitral valve obstruction, values for Ry/v would be expected to rise sharply following mitral valvotomy. Fig. 2 shows the behaviour of Ry/v before and after mitral valvotomy in 27 consecutive cases of mitral stenosis in which mitral regurgitation was judged by the surgeon to be absent both before and after valvotomy. Ry/v increased in 16, decreased in 10, and

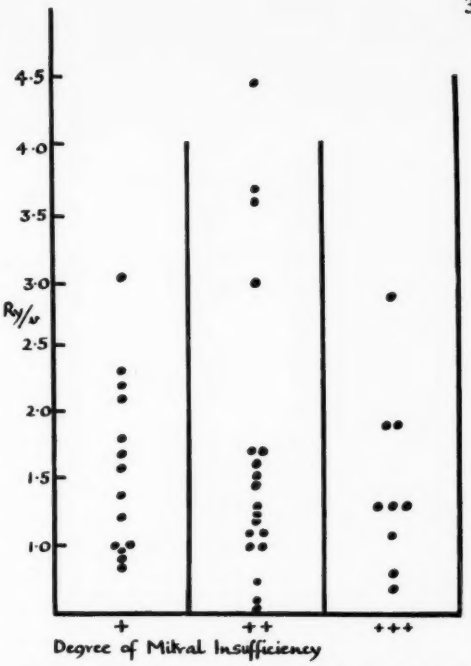
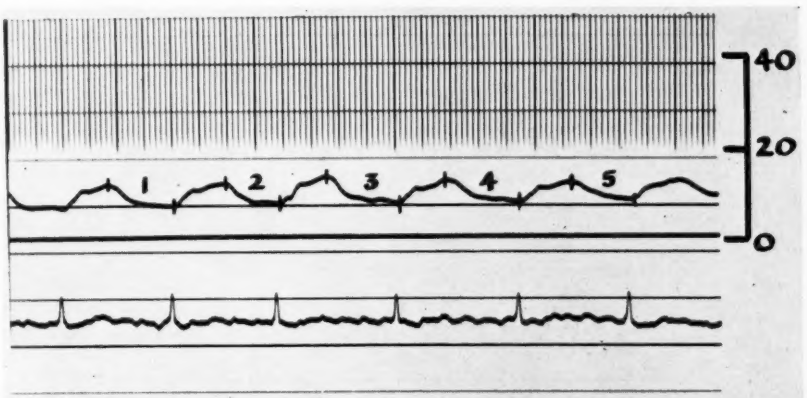


FIG. 4.—Relationship of Ry/v to the degree of mitral regurgitation.



	1	2	3	4	5
t sec	0·48	0·39	0·52	0·53	0·46
RR Interval	0·81	0·76	0·86	0·88	0·78
Ry/v	0·595	0·734	0·722	0·518	0·580

FIG. 5.—Left atrial pressure tracing in a patient with mitral stenosis and atrial fibrillation, showing the variation from one cardiac cycle to another in t and Ry/v.

remained unchanged in 1. Fig. 3 shows an example before and after valvotomy in which Ry/v fell from 2·0 before to 0·71 after valvotomy. It is possible that the manipulation of the heart or left atrial suturing after valvotomy invalidate the immediate post-operative measurements of dynamic left atrial pressure. Certainly there are changes in blood flow associated with an adequate mitral valvotomy, which may invalidate measurement of Ry/v. But the lack of a more consistent change in Ry/v following valvotomy suggests that Ry/v is influenced by many factors other than mitral valve obstruction, and that the measurement is of little value in estimating the adequacy of the valvotomy in the theatre.

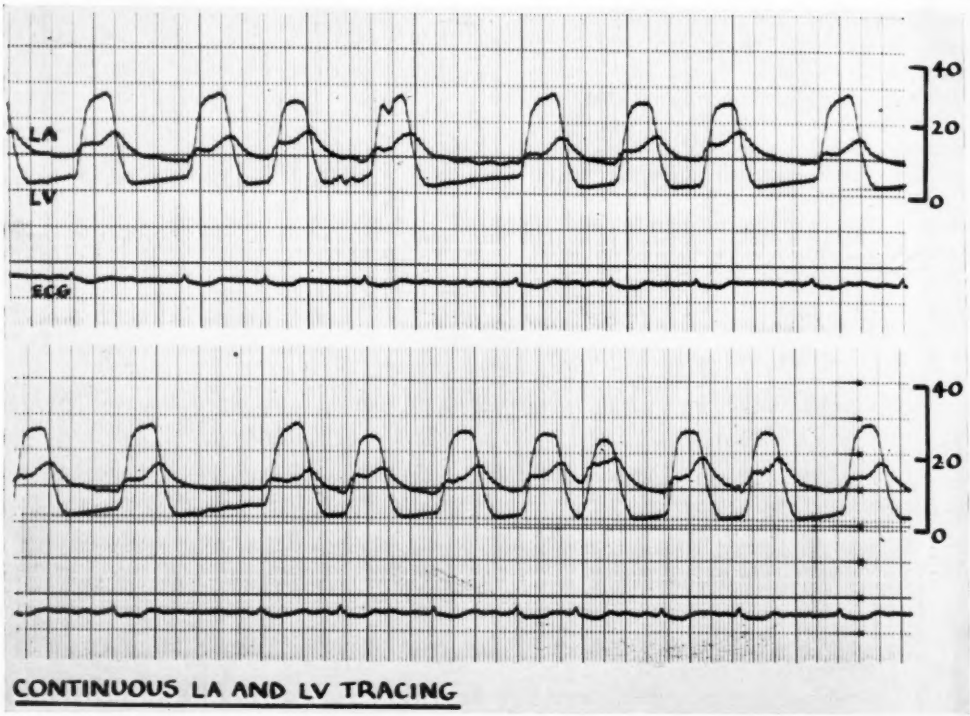


FIG. 6.—Left atrial pressure tracing (0/40) and left ventricular pressure tracing (0/100) with electrocardiogram in a case of mitral stenosis with atrial fibrillation, showing the extreme variations of t with variations in RR interval in the record. See also Fig. 7.

A graph of Ry/v and the degree of mitral regurgitation in 43 patients in whom varying degrees of mitral regurgitation were judged to be present is shown in Fig. 4. There is no correlation between the degree of mitral regurgitation and Ry/v. 42 per cent of the patients with moderate mitral regurgitation have figures for Ry/v of 1·5 or less. Thus Ry/v seems to be of little use in separating the patients with tight mitral stenosis from those with mild stenosis, from those with no stenosis, and from those with various degrees of coexisting mitral regurgitation.

DISCUSSION AND CONCLUSIONS

An analysis of the rate of fall of the diastolic portion of left atrial pressure tracings would seem logically to give a measure of obstruction at the mitral valve. That this, in fact, does not prove to

be the case in practice may be related to several factors. Measurements of small changes in pressure over a short time interval are probably poorly reflected in currently used measuring devices. The factor of blood flow, which is intimately related to pressures recorded (Dickens *et al.*, 1957), is not analysed. The accurate determination of Ry/v in any single pressure tracing is made difficult by the frequent presence of atrial fibrillation and thus differences in cycle lengths and pressure levels (Fig. 5). Even the average of ten consecutive complexes does not seem to be wholly adequate in estimating Ry/v. The time (t2–t1) from the top of the v wave to the end of the fall (y) is a function of heart rate (Fig. 6 and 7); and, since it is a fractional number in the numerator of the Ry/v formula, a small change in time (t) related to heart rate could account for a large change in Ry/v without a change in obstruction of the mitral valve.

The above factors were controlled as carefully as possible in this study. However, the use of Ry/v in individual cases at operation does not seem valuable, since it does not differentiate either the degree of mitral stenosis or the presence or absence of a significant degree of mitral regurgitation under these circumstances. This would cast some doubt on the validity of this formula in other circumstances.

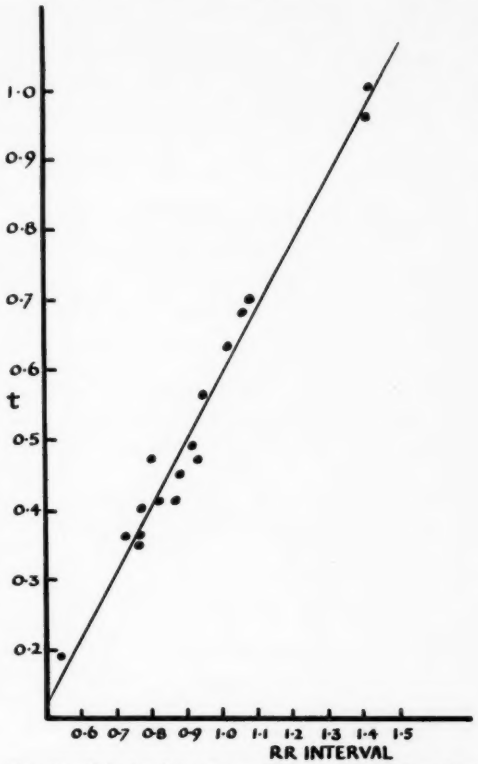


FIG. 7.—Relationship of t and RR interval taken from 17 consecutive cycles in the case illustrated in Fig. 6, showing a linear relationship between t and RR interval.

SUMMARY

An analysis of the diastolic part of left atrial pressure tracings (Ry/v) taken at the time of mitral valvotomy, showed a poor correlation with the degree of mitral obstruction and also with the presence or absence of mitral regurgitation. The measurement of Ry/v at operation was of little or no value in assessment of the degree of mitral obstruction or the adequacy of the valvotomy.

I wish to thank Mr. John Robson of the Department of Surgery for technical assistance in the preparation of this study.

REFERENCES

Connolly, D. C., Thompkins, R. G., Lev, R., Kirklin, J. W., and Wood, E. H. (1953). *Proc. Staff Meet., Mayo Clinic*, **28**, 72.

Dickens, J., Raber, G., Woldow, A., Lorange, G. C., and Goldberg, H. (1957). *New Engl. J. Med.*, **256**, 1017.

Owen, S. G., and Wood, P. (1955). *Brit. Heart J.*, **17**, 41.

EVIDENCE FOR PULMONARY VASOCONSTRICTION IN MAN

BY

RICHARD GORLIN*, FRANK B. CLARE, AND JOSEPH J. ZUSKA

From the U.S. Naval Hospital, Portsmouth, Virginia, U.S.A.

Received October 15, 1957

The occurrence of pulmonary vasomotor activity has been one of the most highly disputed subjects in modern medicine. Probably the most decisive studies of pulmonary vasomotion were those of Daly and his collaborators (1952). Over the course of the last fifteen years by elaborately devised experiments under rigidly controlled conditions, they demonstrated in animals the occurrence of both vasoconstriction and vasodilatation of the pulmonary vascular bed. They showed that vasoconstrictor fibres were unmasked following atropinization and that these fibres ran in the cervical vago-sympathetic chain.

Generalized hypoxia has been stated to cause mild vasoconstriction in normal man (Westcott *et al.*, 1951; Doyle *et al.*, 1952), although unilateral studies have not shown vasoconstriction in the hypoxic lung (Fishman *et al.*, 1955). Similarly, mild vasoconstrictor effects have been attributed to epinephrine by Witham and Fleming (1951), but not to nor-epinephrine (Fowler *et al.*, 1951). The findings in most of these studies have been minimal and some authorities have doubted whether there is major neural and humoral control of the lesser circulation in normal man (Hamilton *et al.*, 1939; Cournand, 1947). On the other hand, an elevated pulmonary vascular resistance may be decreased by an autonomic blocking agent (Fowler *et al.*, 1950); and in mitral stenosis, a rapid partial regression in raised resistance is often seen within the first two to four weeks following successful valvotomy (Dexter *et al.*, 1950; Lukas and Dotter, 1952).

In the course of study of a patient with primary pulmonary hypertension, unexpected acute changes in pulmonary arterial pressure and blood flow were observed. It is the purpose of this report first to present these data and secondly to record the apparent inefficacy of bilateral stellate ganglion block in the treatment of primary pulmonary hypertension.

Case Report

The patient was a 42-year-old, white, married mother of two, who was admitted to this hospital with the chief complaint of chest pain. Except for a single attack of unexplained syncope six years ago she had been in good health until approximately one year before admission, at which time she had a sudden and severe hæmoptysis of approximately one cupful of bright red blood. X-ray revealed diffuse haziness of the right upper lobe which cleared. Bronchoscopy was normal. This event recurred four months prior to admission. During the preceding year the patient noted the erratic occurrence of a poorly localized and poorly described heavy pain over the præcordial and substernal areas, not particularly related to effort and with no radiation. She also noticed mild shortness of breath on exertion but was still able to carry on with her housework until shortly before the admission. She did not experience syncope, frank right heart failure, or cyanosis. Physical examination on admission showed a well-developed, well-nourished woman with blood pressure 105/80, pulse 70, respiration 16. There was no clubbing, cyanosis, nor jugular venous distension. The lungs expanded normally and were normal on percussion and auscultation. The heart showed no enlargement. There was a slight heaving sensation over the pulmonary outflow tract. The pulmonary second sound was much accentuated and louder than the aortic second sound. The first heart

* Present address: Peter Bent Brigham Hospital, Boston, Mass.

sound was normal and there were no murmurs: a third sound was heard in early diastole along the left sternal border. The rest of the physical examination was within normal limits. Electrocardiogram initially showed no abnormalities except that the R/S ratio equalled 0·8 in V1 (Fig. 1). The X-ray of the chest showed a normal heart with enlarged main pulmonary artery and major branches: there was marked diminution in size of the secondary and tertiary branches. An angiocardiogram revealed conspicuous dilatation of the pulmonary artery with arrest of the dye in the main trunk. The dye was then distributed through diminutive branches. During this admission the patient was subjected to cardiac catheterization. The pertinent findings are shown in Table I. To be noted are the normal arterial oxygen saturation, the high

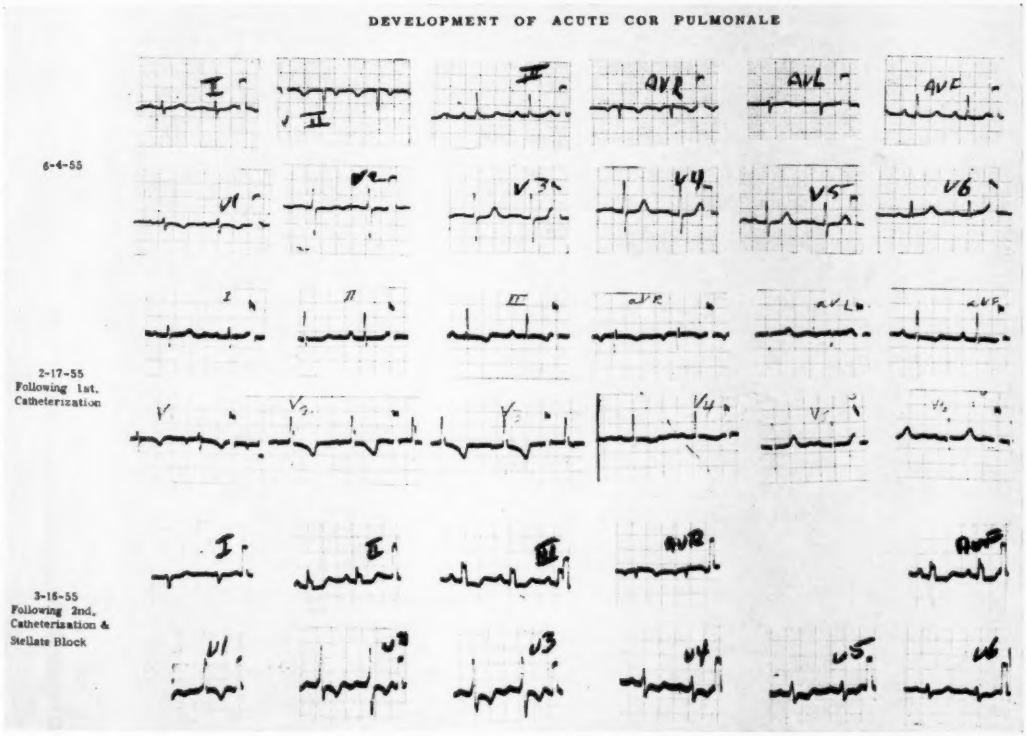


FIG. 1.—Development of acute cor pulmonale. The dates on the left should read 6/4/55, 17/2/56, 16/3/56.

TABLE I

FINDINGS ON CARDIAC CATHETERIZATION DURING TREATMENT OF PULMONARY HYPERTENSION

	Normal rest	17/2/56 rest	Ex.	16/3/56 rest
Arterial O_2 saturation, per cent	96–99	99	100	95
Cardiac output, l/min./m.^{2}	3–4	1·9	2·4	2·7
Pulmonary arterial mean pressure, mm. Hg	12–15	60	78	75
Pulmonary wedge pressure, mm. Hg	5–10	7	5	5
Systemic arterial pressure, mm. Hg	95	95	88	105
Right atrial mean pressure, mm. Hg	0–3	4	8	3
Pulmonary vascular resistance, dynes. sec. cm.$^{-5}$	100	1570	1690	1540

pulmonary arterial pressure with normal pulmonary wedge pressure, the extremely low cardiac output, and the increased pulmonary vascular resistance. During exercise a small increase in output occurred; pulmonary vascular resistance did not change; but the right atrial mean pressure rose while the brachial arterial pressure decreased.

The patient was given priscoline, 100 milligrams orally four times a day for two weeks and intramuscularly for one week. At the end of this time there had been no change in her symptoms, electrocardiogram, or chest X-ray. Cardiac catheterization was repeated and revealed no change in pulmonary arterial pressure or resistance, indicating that priscoline had been ineffective. Because of encouraging reports concerning stellate ganglion block in the treatment of acute pulmonary embolism it was decided to observe the effects of this procedure during cardiac catheterization. A left stellate block was performed with 1 per cent procaine. Observations were made following production of a Horner's sign. Essentially no change occurred in pulmonary arterial pressure or vascular resistance (Fig. 2). Following these measurements a right stellate ganglion block was performed, again with no change in pulmonary hæmodynamics. Considerable needling of the right cervical region was necessary to maintain a block. At this point the patient began to complain of severe anterior chest pain, unaffected by respiration. She was thereupon given 0·6 mg. of nitroglycerin which produced a mild fall in systemic and pulmonary arterial pressures. A Fick cardiac output measured at this time revealed a decrease of 1·2 litres a minute over the control with a calculated rise in both vascular resistances. The pain continued unabated. Observations four minutes

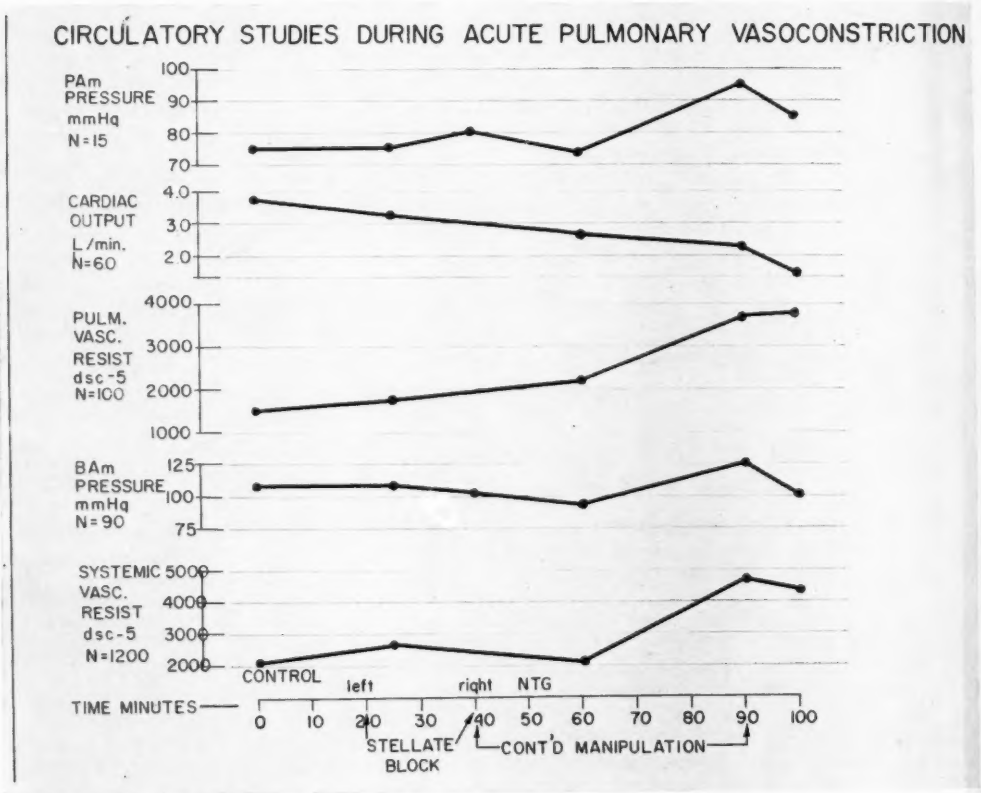


FIG. 2.—Circulatory studies during acute pulmonary vasoconstriction.

following the nitroglycerin revealed a systemic blood pressure of 140/110 with a mean of 125 mm. Hg, pulmonary arterial pressure of 95, pulmonary wedge pressure of 8, a cardiac output of 2·1 litres a minute, and a calculated resistance of 3600 dynes. sec. cm.$^{-5}$. The patient was then given 100 milligrams of demerol, which only partially relieved the pain. Mean systemic blood pressure nevertheless remained at 82 while the cardiac output had further decreased to less than one-half of the control value. The calculated pulmonary vascular resistance had increased to twice the original measurement. Right atrial pressure at this time had risen from 3 to 10 mm. Hg. An electrocardiogram revealed the changes of acute cor pulmonale (Fig. 2). Physical examination and fluoroscopy showed no evidence of gross pneumothorax at this time.

Because of the patient's persistent pain, the failure of relief by stellate ganglion block, and the acute pulmonary hypertension, the procedure was abandoned and the patient returned to the ward where she gradually became more comfortable over the course of the afternoon. Approximately four hours following the procedure, however, she complained bitterly of recurrent chest pain. Physical examination revealed bilateral pneumothorax. 2700 ml. of air were removed from the left and 1000 ml. from the right pleural spaces with needle aspirations controlled by a pneumothorax apparatus and obtaining negative pressures in each pleural space. There was no improvement in the patient's clinical condition and one hour later, despite apparent re-expansion of the lungs, she died suddenly. Pertinent findings at necropsy were limited to the heart and lungs. The heart weighed 250 grams. The right ventricular wall measured 2 to 3 centimetres across. There was stenosis of the right coronary artery. Air escaped from each pleural space when the chest was opened under water. The lung parenchyma was collapsed but otherwise looked normal. The pulmonary vascular bed, however, revealed marked atherosclerosis with plaque formation throughout the larger medium and small branches. There were no gross thrombi or emboli. Microscopic examination revealed intimal thickening in the large pulmonary arteries. The smaller arterioles showed intimal thickening, medial hyalinization, and often fibrous obliteration of the lumen. In some of the small arterioles evidence of organizing thrombus was seen.

Comment

Because of the extremely unfavourable prognosis of primary pulmonary hypertension and the fact that this patient was severely although not yet critically ill with the disease, it was decided to try various forms of therapy. Dresdale *et al.* (1951, 1954) reported that priscoline was effective in lowering pulmonary arterial pressure when administered parenterally as a single dose. Our observations after two weeks' trial indicate this medication was ineffective over that period. Two independent groups of workers reported salutary clinical effects of stellate ganglion block on acute pulmonary embolism (Bageant and Rapee, 1947; Faxon *et al.*, 1951): in some of the cases there was striking relief of pain, dyspnœa and anxiety. A search revealed no previous similar studies in chronic idiopathic pulmonary hypertension. Accordingly, bilateral stellate ganglion block was tried in our patient. A left stellate ganglion block had no effect on the pulmonary vasculature in this patient. While a completely successful right stellate block was not achieved, the actual aggravation of pulmonary hypertension during infiltration and manipulation of this ganglion would at least suggest that bilateral block is also without effect. The failure of this procedure to relieve pulmonary hypertension is similar to the inefficacy of pulmonary plexectomy and thoracic sympathectomy (Griswold; Simeone; personal communications). It is interesting that this latter procedure relieved severe symptoms in two patients although hæmodynamics remained unchanged.

The most striking observation in our patient was the development of pulmonary vasoconstriction within 30 minutes, with a rise in pulmonary arterial pressure and a fall in cardiac output. At the beginning of this response, systemic arterial pressure, systemic vascular resistance, and heart rate were all increased. The association of all these findings together would suggest that (i) a generalized sympathetic discharge had occurred related to pain or to stimulation of cervical autonomic ganglia; (ii) the pulmonary hypertension increased in response to acute left heart failure; and (iii) irritation or puncture of the apical pleura or production of a small radiologically undetectable pneumothorax with the injection needle initiated a nervous reflex resulting in acute pulmonary vascular constriction. The likelihood of sympathetic overactivity is supported by the experimental observations that cervical sympathetic stimulation in the dog results in pulmonary

vasoconstriction (Daly and Hebb, 1952) and that the pulmonary constrictor response to hypoxia is blocked by sympathectomy (Stroud and Rahn, 1953). The second hypothesis is rendered unlikely by the fact that the pulmonary wedge pressure was not raised and that the systemic arterial hypertension receded during the next 30 minutes while the pulmonary vascular obstruction became more severe. No statement can be made concerning the third possibility. Associated with the acute increase in pulmonary obstruction was the development of acute cor pulmonale shown electrocardiographically (Fig. 1) and also hæmodynamically by a rise in right atrial mean pressure.

The authors believe that this is the first time that acute pulmonary constriction unrelated to pharmacological agents or hypoxia has been demonstrated in man under conditions where serial observations of pressures and flows could be made. The acute occurrence of this phenomenon would suggest that more attention be directed to the nervous and humoral factors which may initiate primary pulmonary hypertension. It was the authors' hope to correct the hypertension in this patient before it had progressed to the irreversible and critical stage. That this level was rapidly being approached was shown by the exercise response wherein the systemic blood pressure decreased and the right atrial pressure increased (Howarth and Lowe, 1953). In normal man arterial blood pressure rises and atrial pressure changes little with standard exercise. Findings at necropsy indicated that the disease was more severe than was judged clinically and that little change with autonomic blockade could have been expected.

This study again calls attention to one of the well-known hazards of bilateral stellate ganglion block, namely bilateral pneumothorax. It is believed that the chest pain in this patient was cardiac in origin and not necessarily related to the pneumothorax during the catheterization. Her final demise, however, was undoubtedly related to the sudden recurrence of bilateral tension pneumothorax. As has been pointed out by others (Howarth and Lowe, 1953; Schafer *et al.*, 1956), relatively minor traumata, even after their apparent correction, have been sufficient to cause the death of patients with underlying primary pulmonary hypertension.

Summary

A patient with primary pulmonary hypertension is reported, in whom acute pulmonary vasoconstriction apparently occurred during stellate ganglion block. Observations of pulmonary arterial pressure and flow and calculation of pulmonary vascular resistance were made from data obtained at cardiac catheterization during the procedure. This is believed to be evidence of the occurrence of an acute vascular constriction in the lungs of man.

References

Bageant, W. E., and Rapee, L. A. (1947). *Anesthesiology*, **8**, 500.
Cournand, A. (1947). *Bull. N.Y. Acad. Med.*, **23**, 27.
Daly, I. de B., Duke, H. N., Linzell, J. L., and Weatherall, J. (1952). *Quart. J. Exp. Physiol.*, **37**, 149.
—— and Hebb, C. (1952). *Quart. J. Exp. Physiol.*, **37**, 19.
Dexter, L., Gorlin, R., Lewis, B. M., Haynes, F. W., and Harken, D. E. (1950). *Trans Amer. clin. climat. Ass.*, **62**, 170.
Doyle, J. T., Wilson, J. S., and Warren, J. V. (1952). *Circulation*, **5**, 263.
Dresdale, D. T., Michton, R. T., and Schultz, M. (1954). *Bull. N.Y. Acad. M.*, **30**, 195.
——, Schultz, M., and Michton, R. T. (1951). *Amer. J. Med.*, **11**, 686.
Faxon, H. H., Flynn, J. H., and Anderson, R. M. (1951). *New Engl. J. Med.*, **244**, 586.
Fishman, A. P., Himmelstein, A., and Cournand, A. (1955). *Federation Proc.*, **14**, 48.
Fowler, N. O., Wescott, R. N., Hauenstein, V. D., Scott, R. C., and Mcguire, J. (1950). *J. clin. Invest.*, **29**, 1387.
——, ——, Scott, R. C., and McGuire, J. (1951). *J. clin. Invest.*, **30**, 517.
Griswold, H. A., personal communication.
Hamilton, W. F., Woodbury, R. A., and Vogt, E. (1939). *Amer. J. Physiol.*, **125**, 130.
Howarth, S., and Lowe, J. B. (1953). *Brit. Heart J.*, **15**, 47–54.
Lukas, D. S., and Dotter, C. T. (1952). *Amer. J. Med.*, **12**, 639.
Schafer, H., Blain, J. N., Ceballos, R., and Bing, R. J. (1956). *Ann. intern. Med.*, **44**, 505.
Simeone, F. A., personal communication.
Stroud, R. C., and Rahn, H. (1953). *Amer. J. Physiol.*, **172**, 211.
Westcott, R. N., Fowler, N. O., Scott, R. C., Hauenstein, V. D., and McGuire, J. (1951). *J. clin. Invest.*, **30**, 957.
Witham, A. C., and Fleming, J. W. (1951). *J. clin. Invest.*, **30**, 707.

A SURGICAL STUDY OF COARCTATION OF THE AORTA

BY

ROWAN NICKS

From the Cardio-Thoracic Surgical Unit, Green Lane Hospital, Auckland, New Zealand *

Received June 21, 1957

The object of this study is to present our experience in dealing with coarctation of the aorta and to discuss policy in the management of individual patients who have widely varying ages and symptoms, sometimes complicated by additional lesions. Surgical treatment, which is on a national basis, was developed rather hesitantly at first, but is now practised with confidence. Forty-four cases have been seen since 1948 of whom twenty-seven have received surgical treatment.

Analysis of Necropsy Data for New Zealand

The number of deaths associated with coarctation of the aorta registered in New Zealand and confirmed by necropsy over the past nine years is 28, an average of three cases a year. These have been analysed in Table I. In this series 46 per cent of the deaths occurred in the first year of life and, if these cases are excluded, the average survival was 29 years, 70 per cent of the deaths occurring between 30 and 59 years of age.

TABLE I

Analysis of Deaths from Coarctation in New Zealand, 1947–1955

Age groups	Sex		Total	Cause of death
	M	F		
0–1	7	6	13	Broncho-penumonia in 6 and C.H.F. in 7
2–10	1	1	2	Endarteritis in 1 and post-operative in 1
11–20	3	1	4	Ventricular fibrillation in 2, C.H.F. in 1, and operation in 1
21–30	—	—	—	
31–40	2	2	4	C.H.F. in 2, rupture in 1, and coronary insufficiency in 1
41–60	5	—	5	C.H.F. in 4 and rupture in 1
Totals ..	18	10	28	

C.H.F.=Congestive heart failure.

The true incidence in this necropsy series is impossible to assess accurately as no detailed information as to the number of necropsies performed in New Zealand over the period of study is available, but it is at least one in 3000 deaths, compared with one in 1000 (Blackford, 1927), and one in 1550 (Calodney and Carsen, 1950). The predominance of male to female subjects in both series is in accordance with accepted figures.

* Delivered to the Australasian Cardiac Society, Wellington, March 2, 1956. Author's address: Royal Prince Alfred Hospital, Sydney, Australia.

Clinical Series

We have seen 44 patients, 14 in the first decade, 13 in the second, 10 in the third, 4 in the fourth, 2 in the fifth, and 1 in the sixth decade. This means 3 per 100,000 for the Province of Auckland and rather under 2 per 100,000 for the remainder of North Island and for South Island, but there are no doubt other cases that have not been seen. All our 44 patients were European and no Maoris were seen. The infrequency of recognized coarctation in coloured races has been commented upon by King (1926).

Clinical Presentation. The symptoms have been minor and related to vascular hypertension: on the average, this has not been excessive before fifteen years (about 140 systolic), has risen to a maximum between twenty and thirty years (200/105), and fallen slightly after this. The pressure in individual cases, however, differed little when taken years apart, suggesting that the heart was capable of functioning normally against the resistance until breakdown from congestive heart failure, cerebro-aortic vascular accidents, or endocarditis.

Usually the correct diagnosis was inferred by observing vigorous pulsation in the neck and recognizing delay or absence of the femoral pulses, attention having been drawn to the possibility of coarctation by brachial hypertension or by unexplained systolic murmurs. It was confirmed by clinical evidence of collateral anastomotic vessels, fluoroscopic demonstration of lesser degrees of left ventricular hypertrophy with evidence of aortic constriction indicated by a small or double aortic knuckle, dilatation of the ascending aorta, and notching of the lower ribs from tortuous intercostal arteries, all of these signs being more evident in older cases with more severe degrees of coarctation. The gravity of the obstruction in individual cases has been estimated by the blood pressure, and the degree of cardiac hypertrophy as recorded by serial X-rays and electrocardiograms. Blood pressures have been taken from both brachial arteries to ascertain the site of the lesion in relation to the aortic arch and its branches. In most cases with left ventricular hypertrophy there has been a rounding and elongation of the left ventricle without significant enlargement in the transverse diameter of the heart, the cardio-thoracic index being within normal limits in 33 of the 44 cases, doubtfully enlarged in 4, and moderately increased in 7 cases, three of which were complicated by associated cardiac lesions.

Angiocardiography is regarded more as an interesting record than of great practical value except in unusual cases, and when performed, has merely confirmed visually the presence of a lesion already deduced. The operability in each case has been assessed at thoracotomy. The routine provision of freeze-dried arterial grafts has lessened still further the scope of this examination.

Associated Lesions in the Clinical Series

A *ventricular septal defect* was considered probable in two patients. In one, a child of 8 years, death occurred but no necropsy was available. In the other, a man of 36, the clinical condition has remained satisfactory for three years.

Aortic valve lesions have been found in 7 cases (16 %). In six the presence of a bicuspid aortic valve was suspected: in four it has produced no effect on the dynamics although in two of them there was slight aortic regurgitation which did not interfere with a satisfactory operative result, but in the other two there was serious regurgitation (one complicated by angina pectoris as well), and great cardiac enlargement, so that surgery was not advised. In a girl, aged 16, who had enough aortic regurgitation to produce a blood pressure of 200/70 before operation, the resection was successfully carried out and a year later the aortic regurgitation seemed less as the blood pressure was 155/95. In a man, aged 21, however, with a blood pressure of 165/60, the regurgitation was thought too great to advise operation: four years later, although he was still free from symptoms, the heart had become much larger.

A diagnosis of *subaortic stenosis* was made in a child of eight without symptoms and operation has been deferred until she is older.

Turner's syndrome has occurred in one woman and two adolescents, all of whom have received operative treatment.

Pulmonary emphysema was present in two cases. Resection of the coarctation was undertaken in one of these, a man, aged 21, who also had pulmonary hypertension, 74/40 mm. Hg. He had a stormy convalescence with some congestive heart failure, but improved gradually. A year later he was better with a blood pressure of 150/80 instead of 230/115, but still with right bundle-branch block.

Surgical Treatment

At first the policy was conservative and operation was deferred while the clinical status was satisfactory. After successful relief by operation, even in cases with severe cardiovascular embarrassment, it is now advised in most cases at the appropriate time, and we think this is generally accepted. This policy is illustrated by the histories of two of our patients, one of whom was made sterile to prevent the strain on her coarctation of further pregnancy, and the other rendered impotent by bilateral lumbar sympathectomy (performed elsewhere) on the mistaken diagnosis of essential hypertension.

In the twenty-seven cases between the ages of 9 and 35 years in which surgery has been done, resection has been performed in all. The aorta was reconstituted by end-to-end anastomisis in twenty-four, and by a plastic reconstruction in two. In one patient hæmorrhage from a friable suture line necessitated terminal obliteration of both ends of the aorta, and this patient has survived without much change for over two years. Two cases died from operation (mortality 7%) one from haemorrhage and one from cerebral anoxia. There have been no late deaths.

Complications of Operation. Severe hæmorrhage occurred in three cases apart from the two already described, one from cutting through of the proximal toothed Pott's clamp on the aorta at the medial end (controlled with difficulty), and one each from rupture of an aortic intercostal and a bronchial vessel respectively.

Post-operative chylothorax developed immediately in one cases (necessitating suture of the thoracic duct), temporary recurrent laryngeal palsy in one, and transient pulmonary collapse in two others. One of these last two was complicated by pulmonary hypertension and emphysema, and the collapse and infection induced early cardiac-respiratory failure from which there was a prolonged and stormy convalescence.

Blood Pressure Changes. The blood pressure has been recorded in most cases during and after operation. On application of the clamps above and below the coarctation there was an immediate rise to a high stationary level in the proximal segment if the subclavian artery had not been occluded; but often it continued upwards insidiously during the operation if this vessel were occluded. The hypertension was controlled by raising the trunk or by the administration of an intravenous normal saline drip containing an 0·1 per cent solution of the hypotensive drug arfonad during the period of occlusion. In spite of careful regulation, on occasions the blood pressure was observed to fall precipitately with the exhibition of this drug, but no harm ensued from this.

In the distal segment there was a regular fall in the systolic and diastolic pressure, but a good flow was observed. On release of the clamps after resection and restoration of the aorta there was an immediate fall in both systolic and diastolic blood pressures with equalization across the suture line. In some cases, to maintain and stabilize the blood pressure at the arbitrary systolic level of 100 mm. Hg, it has been useful to lower the upper half of the body and to speed up the blood transfusion for a short period. In one case, already mentioned, hypotension on release of the aortic clamps was considered to have caused irreversible brain damage.

As an illustration, a case aged 10, may be quoted. Before clamping the aorta at operation, the blood pressure was 141/99 proximally and 123/92 distally; during the clamping the difference increased, the figures being 160/111 and 78/74, and after release of this there was a balanced pressure of 116/87 mm. Hg.

Post-operatively the patients have been in a state of vaso-constriction with a variable rise of blood pressure and pulse rate, which has relaxed only gradually. The blood pressure has remained high, sometimes at the same level as before operation, for one to three weeks and has usually not

attained a normal level at the time of discharge. At the follow-up examination (minimum four months), the blood pressure has been reduced to normal in 19, reduced but not to normal in 4, and unchanged in one case in which anastomosis was not accomplished. The temporary persistence of hypertension after restoration of the aortic lumen is thought to be due to vaso-constrictive reflexes attempting to maintain the habitual arterial pressure. Post-operative rupture at the suture line is considered unlikely unless there has been either a technical fault or infection, and our cases have been allowed to walk about as soon as the blood pressure and pulse rate were stabilized.

Results. Of the 29 patients who have had operations, two died and details have been given. None is known to have died since the operation so far, but we have not been able to trace three of them. Nineteen have obtained an excellent result, by which we mean that each is leading a normal life with a normal blood pressure and a normal electrocardiogram. Four others still have some minor restrictions and a small rise of blood pressure, so we have called this a good result instead of excellent. Only one has failed to obtain any improvement.

The Local Pathological Lesion

The coarctation is seen at operation as a localized constriction of the anterior, posterior, and superior aspects of the aortic isthmus adjacent to the insertion of the ligamentum arteriosum. It has been remarkably uniform, differing only from this standard pattern in four cases, one with hypoplasia of the arch, one with a partial constriction extending into the transverse aorta proximal to the subclavian artery, and two with the coarctation just at the origin of this artery (see later). In the adult cases operative resection and anastomosis has been facilitated by the natural lengthening of the vessels in response to hypertension. Examination of the excised specimens in each case has disclosed a diaphragm with a perforation, usually eccentric, that constitutes the sole aortic lumen and is situated at the site of the maximum external narrowing. Distal to this, a jet lesion, described by Edwards (1948) with thickening and irregularity of the intimal surface and with underlying atheroma has been observed. This is important since it is prone to saccular and dissecting aneurysms and is potentially dangerous for suture.

The lumen has been absent in some cases and has varied from a pin-hole up to 4 mm. in diameter in the others. This maximum diameter, found in a case with severe hypertensive symptoms, might represent a critical size that produces enough obstruction to give symptoms. Microscopic sections confirmed a constant thickening of the tunica media which was infiltrated by varying amounts of fibro-elastic tissue and smooth muscle. This actually formed the coarctation diaphragm except for intimal thickening of fibrous tissue at the free margin, indicating that there would be no local weak-

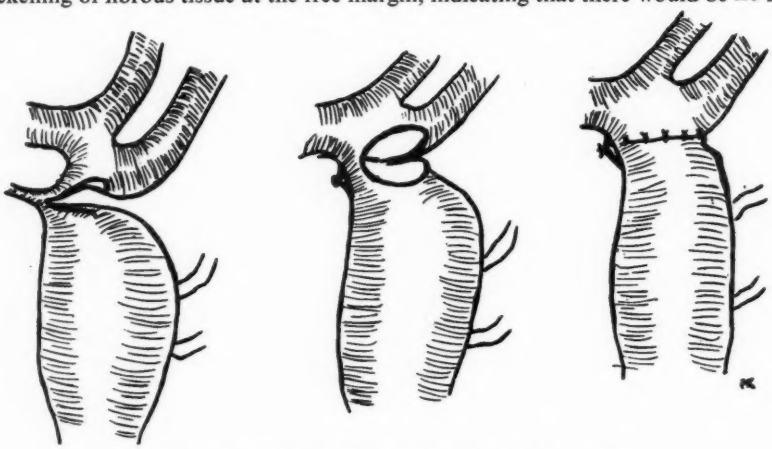


Fig. 1.—Plastic operation for high coarctation (see p. 355).

ness of the aorta if the diaphragm were judiciously excised. The ductus has been patent in only one case: it was small and closely proximal to the coarctation.

These were the usual findings but sometimes, as stated, the coarctation was unusual in site or shape. A man, aged 33, had severe headaches and a blood pressure of 190/110. At operation the coarctation was very high, short, and situated just beyond the subclavian artery, with an almost aneurysmal post-stenotic dilatation beyond (Fig. 1). The subclavian artery and the fusiform vessel lay closely together. A plastic operation excising the coarctation diaphragm from within and restoring the lumen between the subclavian and distal aorta was performed, and his convalescence was uneventful.

In another operation on a boy, aged 13, who had no symptoms and only moderate hypertension, the coarctation was at the origin of the left subclavian artery and extended upwards into the transverse aorta. Surgical relief was accomplished by a plastic operation (Fig. 2), during which the pressures in the aorta were recorded as 180/135 above the clamps and 94/87 below, falling to 130/98 above and 120/97 below immediately after the operation. The blood pressure reading later was 140/95 and the final result at follow-up was excellent.

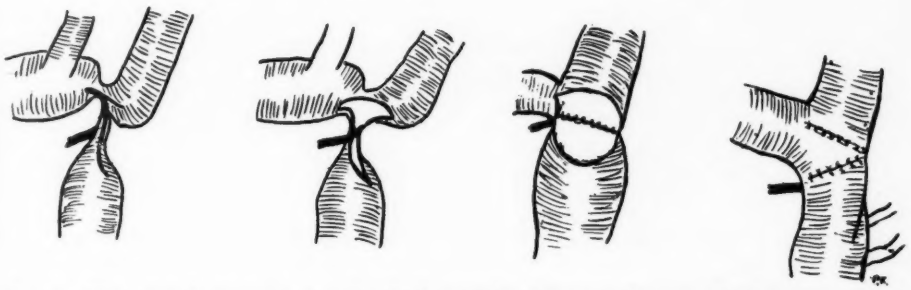


FIG. 2.—Diagrammatic representation of a plastic operation for coarctation extending into the transverse aorta (see text).

DISCUSSION

The single case referred during infancy is noteworthy in view of the deaths recorded during the first year of life (Table I) and of a study of Ober and Moore (1955) who found that ten per cent of deaths from congenital heart disease were from this cause. Mustard *et al.* (1955) in a report on cases of coarctation coming to necropsy at the Children's Hospital, Toronto, found preductal infantile coarctation to be fatal in 89 per cent of cases within three months and the adult type within six months in 60 per cent of their cases. The period of infancy is generally accepted as less critical in localized constrictions of the adult type, as the heart is not subjected to an intolerable strain without a by-pass of collaterals as it is in the atretic group.

In view of these figures, recognition of coarctation in infancy is a challenge so that surgical relief may be considered, despite the risk, in cases of progressive heart failure. The danger of spinal cord damage and of operative shock may be lessened by conducting the operation under hypothermia (Gerbode *et al.*, 1955) at which time the natural elasticity of the tissues permits resection of considerable lengths of atresia and reconstitution of the open ends.

The need for surgical correction (Crafoord and Nylin, 1945) is now more generally accepted. The average predictable life for adults with coarctation, based on post-mortem studies, is between 30 and 35 (Reifenstein *et al.*, 1947; Lewis, 1933), death usually taking place from cardiac failure, vascular accidents, or infective endocarditis and endarteritis. The hazard of a 60 per cent (Claggett *et al.*, 1955) or 74 per cent (Abbott, 1936) chance of death before forty years, even in symptomless cases, seem to justify even the present surgical mortality of 7 per cent from this operation which

has been without serious post-operative complications in most hands and has restored the cardiovascular system towards normal in most cases. Attention has been drawn to the risks of pregnancy in association with coarctation (Mendelson, 1940; Rosenthal, 1955), and to the special danger of rupture in association with a bicuspid aortic valve (Abbott, 1936).

The surgical mortality is reported to be less and the operation has been found technically easier in the young, where the tissues are resilient and the intercostal vessels smaller. Now that the accumulation of cases has been cleared it has been necessary to postulate an age of *elective* operation to anticipate future complications, and this has arbitrarily been chosen at about fourteen years, before hypertension is severe and dangerous, and when the aorta is of such a size that the obstruction will not be significant even if the aorta does not grow at the suture line. Operation has not been withheld at any age if there is impending cardiac or vascular damage. In this series surgery has been deferred in children and in adults with only a moderate rise of blood pressure and no evidence of cardiac strain. It was withheld in two cases (already mentioned) in which severe aortic regurgitation was considered the dominant lesion.

There has been no undue hazard in older cases, even though the vessels and the collaterals were larger; and, indeed, elongation of the vessels resulting from prolonged hypertension has usually enabled approximation with less difficulty. Arterial grafts, although available, have not been necessary, approximation of the ends having been possible in all but one case. Use would be made of a graft if required after excision of a long atretic segment, local vascular damage, or an aneurysm, as recommended by Claggett *et al.* (1955), who reported successful insertion in 4 of 177 cases.

The development of an operation for local excision of the diaphragmatic obstruction and reconstruction of the aorta by local plastic procedures may lower the mortality and give better results in suitable cases, especially in high coarctations involving the aortic arch (Fig. 1 and 2).

Summary

A brief clinical study of 44 consecutive cases of coarctation is presented, together with an analysis of deaths occurring in New Zealand over the past nine years. The beginning of this period coincides with the formation of the Cardiosurgical Unit.

The local pathological malformation is discussed on the basis of operation specimens.

The surgical treatment and follow-up results of 29 cases submitted to surgery are reported. The blood pressure changes during and after operation are described.

Coarctation in infancy is briefly considered and a plea raised for the early diagnosis and surgical treatment of this condition in cases suffering from progressive heart failure. An arbitrary age of fourteen years is put forward as the time of election for routine surgery, to be varied with individual circumstances, and evidence of cardiovascular breakdown. A local plastic operation is recommended for high coarctation in the region of the aortic arch.

The author wishes to thank the members of the Cardiosurgical Unit for permission to discuss these cases. The operations were performed by Mr. Douglas Robb or the author. The follow-up was facilitated by help from Mr. D. Cole, Dr. P. Molloy, and Miss P. Kerkin.

References

Abbott, M. E. (1936). *Atlas of Congenital Heart Disease.* American Heart Association.
Blackford, L. M. (1927). *Collect. Papers Mayo Clin.*, **19**, 686.
Calodney, M. M., and Carson, M. (1950). *J. Pediat.*, **37**, 46.
Clagett, O. T., Kirklin, J. W., and Ellis, F. H. (1955). *Surg. Clin. N. Amer.*, **35**, 937.
Crafoord, C., and Nylin, G. (1945). *J. thorac. Surg.*, **14**, 347.
Edwards, J. E. (1948). *Proc. Staff. Med. Mayo Clin.*, **23**, 108.
Gerbode, F., Purdy, A., Alway, R. H., Piel, J. J., and Da Costa, I. A. (1955). *Amer. J. Surg.*, **89**, 1138.
King, J. T. (1926). *Arch. intern. Med.*, **38**, 69.
Lewis, T. (1933). *Heart*, **16**, 205.
Mendelson, C. L. (1940). *Amer. J. Obstet. Gynec.*, **39**, 1014.
Mustard, W. T., Rowe, R. D., Keith, J. D., and Sirek, A. (1955). *Ann. Surg.*, **141**, 429.
Ober, W. B., and Moore, T. E., Jr. (1955). *New Zealand J. Med.*, **253**, 271.
Reifenstein, G. H., Levine, S. A., and Cross, R. E. (1947). *Amer. Heart J.*, **33**, 146.
Rosenthal, L. (1955). *Brit. med. J.*, **1**, 16.
Tubbs, O. S. (1955). *Brit. med. Bull.*, **11**, 197.

ELECTROCARDIOGRAMS WITH SHORT P–R INTERVAL AND ABERRANT QRS COMPLEX

BY

L. M. SANGHVI AND S. N. MISRA

From the Department of Cardiology, Sawai Man Singh Hospital and Medical College, Jaipur, India

Received September 7, 1957

Electrocardiograms with short P–R intervals and aberrant QRS complexes (WPW beats), characteristic of the classical congenital Wolff-Parkinson-White syndrome, have been reported in hypertension, in arteriosclerotic and rheumatic heart disease, during cardiac catheterization and pneumonectomy, and after administration of digitalis and strophanthin. Borduas *et al.* (1955) noted the frequent clinical occurrence of beats with a short P–R interval and normal or abnormal QRS which were obviously not of the classical type. Hoffman *et al.* (1956) reported five instances of WPW aberration in patients with arteriosclerotic heart disease seen during a two-year period at three active hospitals, only one being an example of the classical type. Four cases with the acquired type of WPW beats associated with certain uncommon features in the electrocardiogram are here reported.

Case Reports

Case 1. A 30-year-old man was admitted because of cough, exertional dyspnœa, palpitation, and præcordial ache of fifteen days' duration. He had had attacks of joint pains at intervals for five years. On examination, he had rheumatic aortic regurgitation and early congestive failure. The heart was moderately enlarged with left ventricular configuration on fluoroscopy. The blood pressure was 110/55.

The electrocardiogram (Fig. 1) showed a pattern of left ventricular strain with inverted T waves in leads I, aVL, and V4–6. The sinus rate varied between 115 and 125 a minute (R–R 0·48–0·52) and

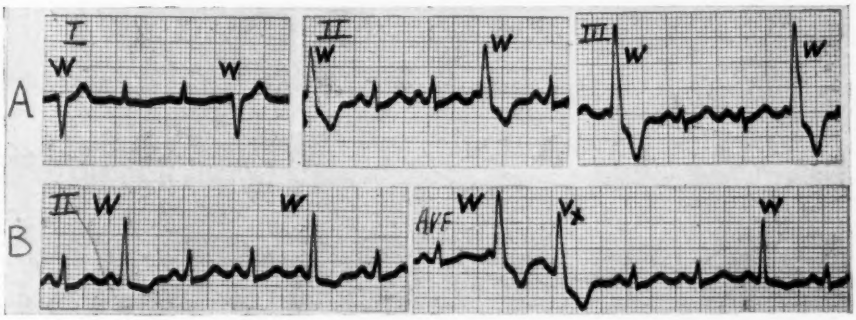


Fig. 1.—Case 1. Electrocardiogram, showing WPW complexes produced by parasystolic rhythm.

in the sinus beats the P–R interval was 0·16 and the QRS duration 0·07 sec. In record A aberrant complexes with short P–R interval (W) occur after every two sinus beats at intervals of 1·46–1·50 sec. (i.e. $3 \times 0{\cdot}50 = 1{\cdot}50$) giving rise to a trigeminal rhythm. In record B, obtained soon after A, the R–R

interval between successive WPW beats was either 1·50 sec. (lead II) or 2·10 sec. (aVF). In these leads there are WPW beats with a QRS duration not exceeding that in sinus beats (0·07 sec.), and a P–R interval of 0·14 sec. There is a premature complex in aVF (V_x) similar in contour to the QRS of the preceding WPW beat. A similar complex is seen in aVL. Numerous premature complexes from another focus were seen in lead I (not shown in figure). In the WPW beats in this case, the P–R interval varied from 0·07 to 0·14 sec., QRS duration from 0·07 to 0·10 sec., and the P–S duration from 0·18 to 0·21 sec. The QRS contour also varied greatly.

Case 2. A 57-year-old man was admitted unconscious with a history of cough and dyspnœa for three months, and aphasia and hemiplegia of the right side for two months. Oedema of the feet and ascites had developed 15 days before and he had been unconscious for seven days. On examination, he had Cheyne-Stokes respiration, generalized anasarca and ascites, grossly enlarged liver, and irregular heart rhythm with a rate of about 100 a minute; the blood pressure was 130/100, and hemiplegia of the right side was present. At the apex the heart sounds were faint and there was a protodiastolic gallop; the aortic and pulmonary second sounds were accentuated. Laboratory examination showed normal urine and cerebrospinal fluid, negative Kahn test, and blood urea 35 mg. per 100 ml. Clinically the diagnosis was myocardial infarction followed later by cerebral embolism and congestive failure. The patient died on the eighth day after admission. Autopsy could not be obtained.

The electrocardiogram (Fig. 2) revealed a pattern of left ventricular strain with inverted T waves in leads I, aVL, and V5–6 and QS deflections in V1–3 suggestive of old anteroseptal infarction. The

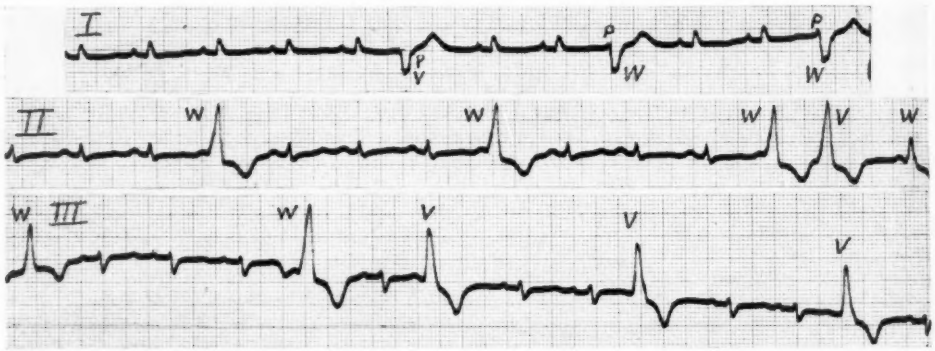


FIG. 2.—Case 2. Electrocardiogram, showing WPW complexes produced by parasystolic rhythm with fusion beats.

sinus rate was 97 a minute and in the sinus beats the P–R interval was 0·18 and QRS duration 0·10 sec. Lead I shows a premature complex and two WPW beats with similar QRS contour and duration of 0·14 sec., at intervals of 1·88 sec. The latter two closely follow a P wave after a P–R interval of 0·04 and 0·06 sec., respectively. In leads II and III WPW/beats occur at intervals of 2·48 sec. (2 × 1·24) except the last beat in lead II which occurs after 1·24 sec. In lead III there are also premature complexes at intervals of 1·88 sec. Other leads showed WPW beats or premature complexes at regular intervals. The P–R interval was 0·14 and the QRS duration 0·10 sec. in the last WPW beat in lead II, while they were 0·13 and 0·11 sec. respectively in the first WPW beat in lead III. In the WPW beats in this case the P–R interval varied from 0·04 to 0·14, QRS duration from 0·10 to 0·14, and P–S duration from 0·18 to 0·24 sec. Long strips showed WPW beats with variable coupling at intervals of 1·24 or 2·48 or 3·80 (3 × 1·24) sec. and premature complexes at intervals of 1·88 sec.

Comment. In the above two cases there were premature complexes with a short P–R interval (WPW) and others without a preceding P wave. Diagnosis of genuine WPW beats of the classical

syndrome is usually made when (i) the aberrant QRS has an initial slow rising slurred delta wave; (ii) the short P–R interval of these beats does not change regardless of the cycle length; and (iii) such beats occur in at least two successive cycles (Katz and Pick, 1956). In these cases, though a delta wave was present in some of the beats, the latter two criteria were absent. Again the wide variation of the P–R interval and of QRS duration and contour in most of these beats, and the presence of other premature complexes in the same record left little doubt that the beats were ventricular fusion complexes (except in Case 2, lead I) resulting from interference between ectopic impulse and a sinus impulse in the ventricles. That this ectopic impulse originated in a parasystolic centre was demonstrated by (i) the R–R intervals between successive WPW beats being multiples of a common denominator and (ii) the variation of the coupling of these beats, the QRS complexes occurring at different times in the cardiac cycle.

In Case 2 a second parasystolic centre caused aberrant complexes at regular intervals. In some of these (lead I) the QRS closely follows a P wave at an interval of less than 0·07 sec. which is considered to be the minimum conduction time from the S-A node to A-V node, and its duration and contour is similar to the premature complex without a P wave. These WPW beats, therefore, though preceded by a P wave, are pure ectopic complexes occurring very prematurely and not fusion beats. Occurrence of premature complexes similar to the fusion complex in Case 1 is difficult to explain.

Case 3. A 52-year-old man had acute infarction of the diaphragmatic surface of the heart in June 1955. A routine cardiogram (Fig. 3) showed Q waves and inverted T waves in leads II, III, and

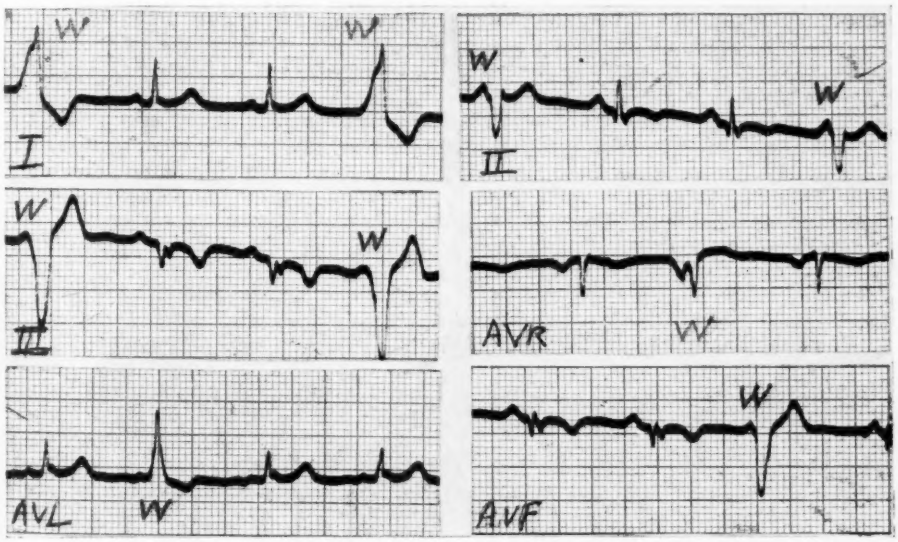


FIG. 3.—Case 3. Electrocardiogram, showing WPW complexes produced by parasystolic rhythm.

aVF as evidence of old infarction. The sinus rate was 83–88 a minute and in the sinus beats the P–R interval was 0·16 and QRS duration 0·10 sec. Aberrant complexes occur after every two sinus beats at intervals of 2·08–2·20 sec. giving rise to a trigeminal rhythm. In leads II, III, aVL and a VF a short P–R interval is easily recognizable in these beats. In other leads measurement of the R–P and the R–R intervals between the sinus beat and the following aberrant complex reveals that the QRS is superimposed upon the initial P deflection, thus showing that the aberrant complexes are in fact WPW beats. In the WPW beats in this case, the P–R interval varies from 0·07 to 0·14 and the QRS

duration from 0·10 to 0·16 sec. The coupling of the QRS complex of these beats to the precedings sinus beat varied greatly.

Comment. A long tracing obtained in this patient showed that, as in the preceding two cases, the aberrant complexes were ventricular fusion beats resulting from ectopic impulse formation in a parasystolic centre.

Case 4. A 30-year-old woman was admitted with rheumatic mitral stenosis and congestive failure. The heart was considerably enlarged, the blood pressure was 95/75, and the electrocardiogram showed sinus rhythm with a pattern of right ventricular strain. She was given nine tablets of digoxin in the next three days, and mercurial diuretics. Four days later there were premature beats and digoxin was stopped. Nine days afterwards a bigeminal rhythm with short runs of tachycardia was noted.

The electrocardiogram (Fig. 4) showed a bigeminal rhythm with alternate WPW beats. The P

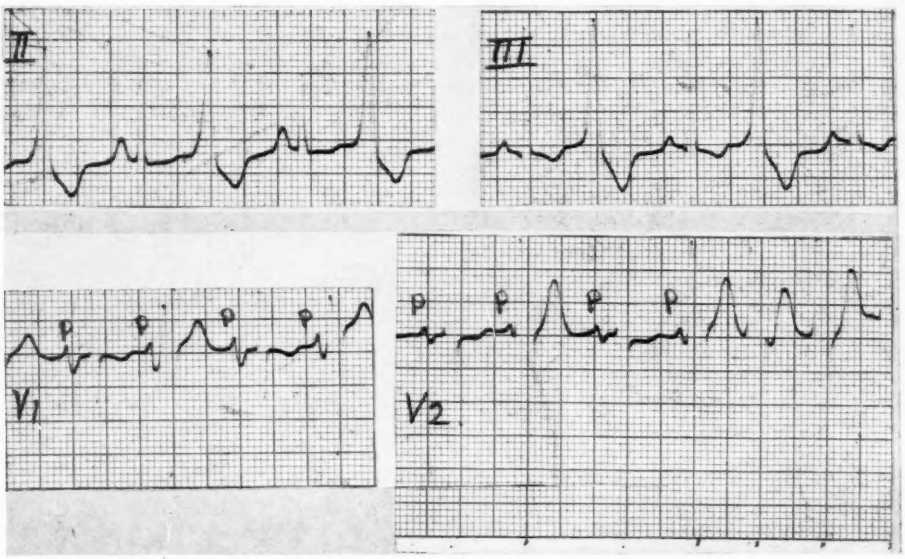


FIG. 4.—Case 4. Electrocardiogram, showing WPW syndrome with paroxysms of auricular tachycardia.

waves and the short P–R interval were not recognizable in the limb leads but were revealed in the præcordial leads, showing that in the former the earlier part of the QRS was formed by the P waves. In sinus beats the P–R interval was 0·16 and QRS duration 0·07 sec. while in WPW beats they were 0·07 and 0·13 sec. respectively. Lead V2 showed a paroxysm of tachycardia with a rate of 144 a minute, beginning with a WPW beat and with aberrant QRS similar to WPW beats in this lead, which terminated in V3. Ventricular premature complexes were seen in lead V4.

Comment. The paroxysm of tachycardia in this case appeared to be supra-ventricular in origin as it started with a WPW beat and its QRS complexes were similar to those of the WPW beats in the same lead. This, as well as the absence of variation of the P–R interval and of the QRS duration and contour, suggested that the WPW beats here resulted from an anomaly of impulse conduction and not of impulse formation as was seen in the first three cases. Fusion beats, however, cannot be ruled out, because of the presence of ventricular premature complexes in the same record and in preceding records, and of a shorter P–S duration in these beats than in the sinus beats.

Discussion

The four cases reported here were from a total of twelve patients with WPW beats seen at this hospital within a period of eighteen months. Of these only one was an example of the classical WPW syndrome. The occurrence of the acquired type was therefore strikingly frequent.

It is generally agreed that pre-excitation of a small fraction of the ventricular musculature is responsible for beats with short P–R interval and aberrant QRS complex. In the genuine WPW beats the impulse causing this pre-excitation originates in the S-A node. Beats of this type, however, occur unquestionably when the ventricle is stimulated from any ectopic ventricular focus (Borduas *et al.*, 1955). If this stimulus occurs later in diastole, it interferes with the sinus impulse in the ventricles giving rise to fusion beats. Similarity of fusion beats caused by ectopic impulse formation and those caused by pre-excitation may be very close (Pick and Katz, 1955).

There seemed little doubt that in the first three cases the WPW beats resulted from ectopic impulse formation and were mostly fusion beats with variable P–R interval and QRS duration and contour; in general the shorter the P–R interval the greater the QRS duration. Butterworth and Poindexter (1944) demonstrated this experimentally by producing varying shapes of fusion complexes by spacing the second ventricular stimulus at various time intervals in the cardiac cycle. Some of the WPW beats were, however, pure ectopic complexes (Case 2, lead I), the QRS occurring very prematurely and closely following the P wave. In the first three cases the ectopic impulse originated in a parasystolic centre. In Case 1 this centre had the same rate of impulse formation as the sinus pacemaker. A similar rate of ectopic and sinus rhythm has been observed in dogs (Scherf, 1926) and in experimental parasystole (Scherf and Chick, 1951), and has been considered to be the cause of pre-excitation beats during cardiac catheterization (Scherf *et al.*, 1952).

The QRS duration in some WPW and premature beats was 0·10 sec. or less, being the same as the sinus QRS (Cases 1, 2, 3). A nodal origin of these beats is obviously out of the question because of the presence of the sinus type of P wave and the aberrant QRST, and of ventricular premature beats in the tracings. Again, a nodal type of parasystole usually occurs in subjects with normal electrocardiograms whereas the ventricular type is usually observed when the tracing is otherwise abnormal (Katz and Pick, 1956). The impulse in these beats presumably originated in the inter-ventricular septum or in a focus equidistant from both the ventricular muscle masses.

The P–S interval in the WPW beats in the first, second, and fourth cases was shorter than that in the sinus beats in the same patient. Such instances, though observed by Kossman and Goldberg (1947) and Wolff and White (1948), have been considered rare (Prinzmetal *et al.*, 1952). In these three cases (except Case 2, lead I) this could not be attributed to a pure ectopic septal or ventricular impulse occurring very prematurely (Prinzmetal *et al.*, 1952) and the possibility that the ectopic impulse in some way accelerates the conduction of the sinus impulse has to be considered. The shorter P–S interval in Case 2, lead I, however, was due to a very premature septal or ventricular impulse.

The third and fourth cases show that the WPW character of the beats may be recognizable in some leads only. Borduas *et al.* (1955) illustrated a case in which only the direct auricular lead showed the shorter P–R interval.

The electrocardiographic findings in three of the four cases reported here illustrate the importance of ectopic impulse formation in the causation of WPW beats of acquired origin.

Summary

Four cases showing electrocardiograms with short P–R interval and aberrant QRS complex of acquired origin are reported.

In three of them there seemed little doubt that the abnormal beats resulted from ectopic impulse formation in parasystolic centres. The beats were mostly fusion beats while some were pure ectopic complexes occurring very prematurely. In these three cases the QRS duration of some of the beats was 0·10 sec. or less, being either the same or less than the sinus QRS, suggesting their origin in the inter-ventricular septum or in a focus equidistant from both the ventricular muscle masses. In two instances the short P–R interval was recognizable in some leads only.

It is suggested that ectopic impulse formation is an important cause of WPW beats of acquired origin.

Dr. L. R. Sarin, Superintendent, S.M.S. Hospital, kindly permitted the publication of this report.

REFERENCES

Borduas, J. L., Rakita, L., Kennamer, R., and Prinzmetal, M. (1955). *Circulation*, **11**, 69.
Butterworth, J. S., and Poindexter, C. A. (1944). *Amer. Heart J.*, **28**, 149.
Hoffman, I., Morris, M. H., Friedfeld, L., and Gittler, D. (1956). *Brit. Heart J.*, **18**, 301.
Katz, L. N., and Pick, A. (1956). *Clinical Electrocardiography, Part I. The Arrhythmias*. Lea & Febiger, Philadelphia.
Kossman, C. E., and Goldberg, H. H. (1947). *Amer. Heart J.*, **33**, 308.
Pick, A., and Katz, L. N. (1955). *Amer. J. Med.*, **19**, 759.
Prinzmetal, M., Kennamer, R., Corday, E., Osborne, J. M., Fields, J., and Smith, L. A. (1952). *Accelerated Conduction: The Wolff-Parkinson-White Syndrome and Related Conditions*. Grune & Stratton, New York.
Scherf, D. (1926). *Z. gis. exp. Med.*, **51**, 816. Cited by Scherf, D., and Schott, A. (1953). *Extrasystoles and Allied Arrhythmias*. William Heinemann, London.
——, Blumenfeld, S., and Mueller, P. (1952). *Amer. Heart J.*, **43**, 829
, and Chick, F. B. (1951). *Amer. Heart J.*, **42**, 212.
Wolff, L., and White, P. D. (1948). *Arch. intern. Med.*, **82**, 446.

VENTRICULAR SEPTAL DEFECT WITH PULMONARY STENOSIS AND AORTIC REGURGITATION

BY

D. M. COLLINS, T. EAST, M. P. GODFREY, P. HARRIS, AND S. ORAM

From the Cardiological Department, King's College Hospital

Received October 17, 1957

The combination of ventricular septal defect and pulmonary stenosis with a left-to-right shunt is well recognized (Abrahams and Wood, 1951). These cases differ from the tetralogy of Fallot in that they are acyanotic, there is no dextroposition of the aorta, and the pulmonary blood flow is increased. Ventricular septal defect may also be associated with aortic regurgitation. The earliest reference to this association which we have been able to trace is that of Breccia (1906). Bret (1956) describes cases of Fallot's tetralogy complicated by aortic regurgitation. However, to the best of our knowledge the combination of ventricular septal defect, pulmonary stenosis and aortic regurgitation with a left-to-right shunt has not been described. We wish to report three patients in whom we believe this combination of congenital cardiac defects exists.

Case Reports

Case 1. The patient was an unmarried woman, aged 20. A congenital heart lesion had been diagnosed two weeks after birth, and during childhood she was forbidden games. However, her capacity for exercise did not appear to have been limited, and she took part in normal activities out of school hours without distress. At the age of 14 she had suffered from fainting attacks, but these were not related to exertion. She had never been cyanosed. There was no history of rheumatic fever. When first seen in February 1953 there was no disability. The jugular venous pulse was normal. There was prominent arterial pulsation in the neck. The radial pulse was regular and collapsing, the blood pressure being 140/50. The apex beat was in the left mid-clavicular line and of normal character. No right ventricular pulsation could be felt. A faint systolic thrill was palpable in the second left intercostal space, and this was associated with a harsh systolic murmur loudest in the pulmonary area, but audible all over the præcordium. A long blowing diastolic murmur commencing with the second sound could be heard in all areas. The pulmonary second sound was very faint.

The electrocardiogram (Fig. 1) and X-ray appearances were normal. The findings at cardiac catheterization are summarized in Table I. The pressure in the pulmonary artery was normal (25/12), but the right ventricular systolic pressure was slightly increased (47 mm. Hg). The withdrawal tracing showed that the change in pressure occurred abruptly at the level of the pulmonary valve, and thus indicated the presence of pulmonary valvular stenosis. The oxygen content of the blood in the pulmonary artery was substantially greater than that in the right atruim and venæ cavæ. The oxygen content of the blood sample taken high in the right ventricle was also increased. At the time these findings were thought to indicate a left-to-right shunt through a patent ductus arteriosus, the increased oxygen content of the blood high in the right ventricle being due either to pulmonary regurgitation or to a co-existing ventricular septal defect. The wide pulse pressure in the systemic arteries appeared to support the diagnosis of a patent ductus.

There was thought to be sufficient evidence to justify thoracotomy with a view to ligation of a patent ductus arteriosus. In March, 1953, operation was performed by Mr. Selwyn Taylor. A coarse systolic thrill was palpable over the base of the pulmonary artery. The suspected ductus arteriosus felt solid; on division it was obvious that the lumen was not patent.

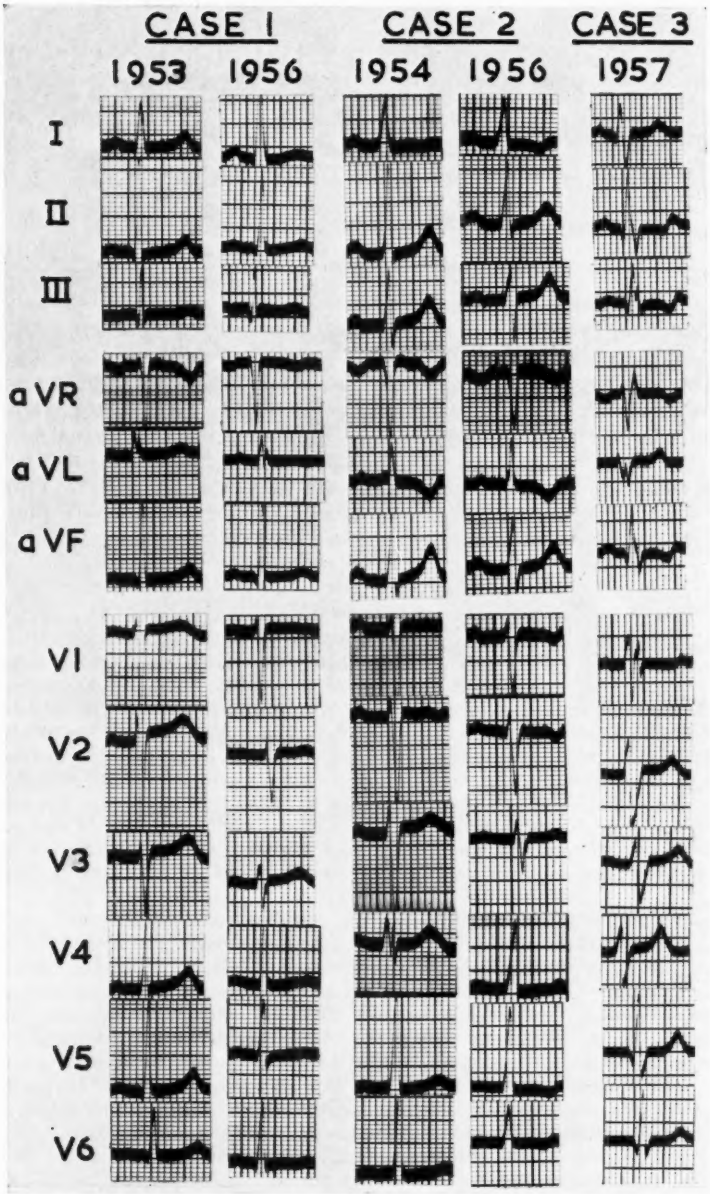


FIG. 1.—Electrocardiograms of the three cases.

TABLE I

DATA OBTAINED AT CARDIAC CATHETERIZATION IN THREE PATIENTS WITH V.S.D., PULMONARY STENOSIS, AND AORTIC REGURGITATION

	Case 1. Woman 20 years			Case 2. Woman 24 years			Case 3. Man 27 years		
PRESSURE READINGS (mm. Hg) Zero at table level	Systolic	Diastolic	Mean	Systolic	Diastolic	Mean	Systolic	Diastolic	Mean
Right atrium	—	—	7	—	—	7	"a"=32		20
Right ventricle	47	14	—	77	9	—	130	20	—
Main pulmonary artery	25	12	19	48	20	36	55	25	39
Pulmonary artery wedge	—	—	15	—	—	—	—	—	23
Femoral artery	114	38	—	150	30	—	180	32	—
BLOOD SAMPLES	Oxygen content (volume %)	Percentage oxygen saturation		Oxygen content (volume %)	Percentage oxygen saturation		Oxygen content (volume %)	Percentage oxygen saturation	
Superior vena cava	14·5	74		12·9	75		18·1	81	
Inferior vena cava	14·5	74		11·0	64		—	—	
Right atruim	11·8	60		13·1	76		18·1	81	
				12·2	71				
Low right ventricle	—	—		13·1	76		18·6	83	
							18·8	83	
Mid right ventricle	15·0	77		—	—		—	—	
High right ventricle	16·3	83		16·8	98		91·1	85	
							19·5	87	
Main pulmonary artery	16·2	83		15·6	91		19·5	87	
	17·2	88							
Right pulmonary artery	—	—		15·8	92		19·5	87	
Left pulmonary artery	17·2	88		15·8	92		—	—	
Pulmonary artery wedge	—	—		—	—		22·3	99	
Femoral artery	19·0	97		17·0	99		21·6	96	
CARDIAC OUTPUT (litres/minute)	2·7			6·0			6·6		
PULMONARY BLOOD FLOW (litres/minute)	8·3			20·0			10·9		
PULMONARY ARTERIOLAR RESISTANCE (dynes sec. cm. $^{5-}$)	39			—			117		

The patient remained well until January, 1956, when she had an attack of bronchitis associated with orthopnœa and on three occasions specks of blood appeared in the sputum. Since then she has become breathless on exertion. The heart is now enlarged and the apex beat is of the left ventricular type. The X-ray taken immediately after operation showed the heart to be of normal shape and size (Fig. 2A) but in July, 1956, there was generalized cardiac enlargement, particularly affecting the left ventricle, and an increase in size of the main pulmonary artery and its branches (Fig. 2B). The electrocardiogram now showed flattening of the T waves in leads V4, V5, and V6 (Fig. 1).

Case 2. The patient was a married woman, aged 24. A heart lesion was discovered during infancy and as a child she was made to spend long periods in bed. She thought that she had always been breathless on exertion. At the age of 19 she had an hæmoptysis and tubercle bacilli were found in the sputum. She spent nearly one year in a sanatorium where a right artificial pneumothorax was induced but abandoned after three months. Since that time she had been more short of breath on exertion, and had been subject to recurrent attacks of palpitation, consisting of regular tachycardia, associated with pain spreading across the chest and down the left arm. There was a long history of neurosis, and she had been under the care of a psychiatrist. There was no history of rheumatic fever. When examined in 1954 she was of asthenic build, with a high arched palate and long thin fingers. There was no cyanosis or finger clubbing. The jugular venous pulse was normal. The radial pulse was regular and collapsing, the blood pressure being 125/45. A sustained apex beat was felt external to the mid-clavicular line, and there was prominent right

ventricular pulsation to the left of the sternum. Systolic and diastolic thrills were palpable to the left o the sternum, and were of greatest intensity in the third and fourth left intercostal spaces. Over the entir præcordium a harsh systolic murmur was heard, loudest in the fourth left space. An equally harsh murmur starting with the second sound and occupying almost the whole of diastole, was audible in all area but loudest in the fourth left intercostal space. In the third left intercostal space the murmur sounde roaring and continuous. The aortic second sound was of normal intensity, but the pulmonary second soun was very soft.

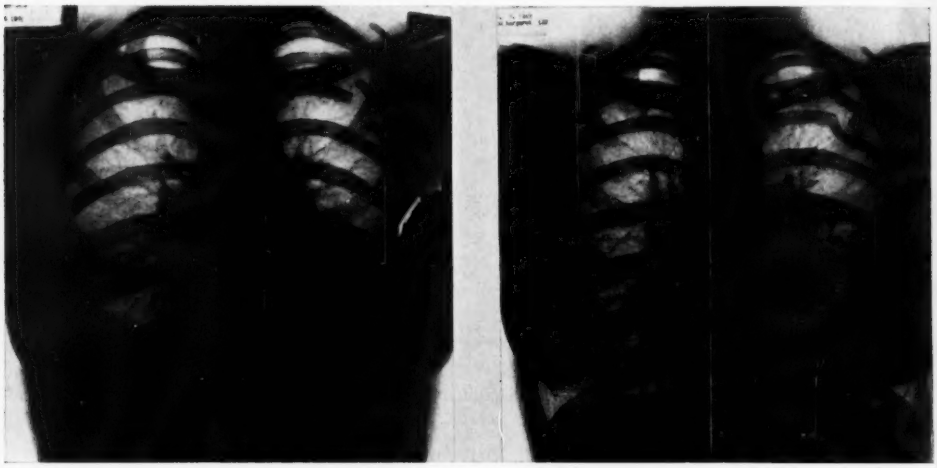


FIG. 2.—X-ray of Case 1. (A) 1953: heart normal. (B) 1956: showing generalized enlargement, especially of the left ventricle and increase in size of the pulmonary artery and its branches.

The electrocardiogram suggested left ventricular hypertrophy. The T waves were inverted in VI biphasic in I, and of low voltage in V5 and V6 (Fig. 1). X-ray of the chest (Fig. 3A) showed evidence of ol tuberculosis in the right upper lobe. There was generalized enlargement of the heart, particularly affectin the left ventricle, and the arterial shadows in the lungs were unduly prominent.

Cardiac catheterization (Table I) showed an increase in the pulmonary artery pressure (48/20), and o withdrawal of the catheter a pulmonary infundibular stenosis was demonstrated, the systolic pressure i the main right ventricle being 77 mm. Hg. The blood in the pulmonary artery, and in one sample from th right ventricle, was excessively oxygenated. The evidence again suggested that the shunt from left to righ was due to a communication between the aorta and pulmonary artery, the most likely cause of which woul be a patent ductus arteriosus.

Thoracotomy was carried out by Mr. W. P. Cleland on November 2, 1954. A patent ductus arteriosu was not present. No abnormality of the aorta could be demonstrated. The aorta and pulmonary arter were separated to within 12 mm. of their origins, and no "window" could be felt between the vessels. A operation the thrill at the base of the heart seemed to be continuous.

Following the operation the patient has gradually become more breathless on exertion. In Novembe 1956, an attack of bronchitis occurred and subsequently she has been unable to walk for more than 30 yard without dyspnœa; she requires four pillows at night. The heart has increased in size (Fig. 3B) and th electrocardiogram shows evidence of deterioration of the left ventricle (Fig. 1).

Case 3. A married man, aged 27, was found to have a heart lesion at birth. However, he led a norm life, rowed in his school eight, and played all games. There was no history of rheumatic fever. He ha never been cyanosed. His father was said to have a heart lesion. For two years he had noticed slig diminution in his athletic ability, but was still able to run for a bus and to climb stairs two at a time.

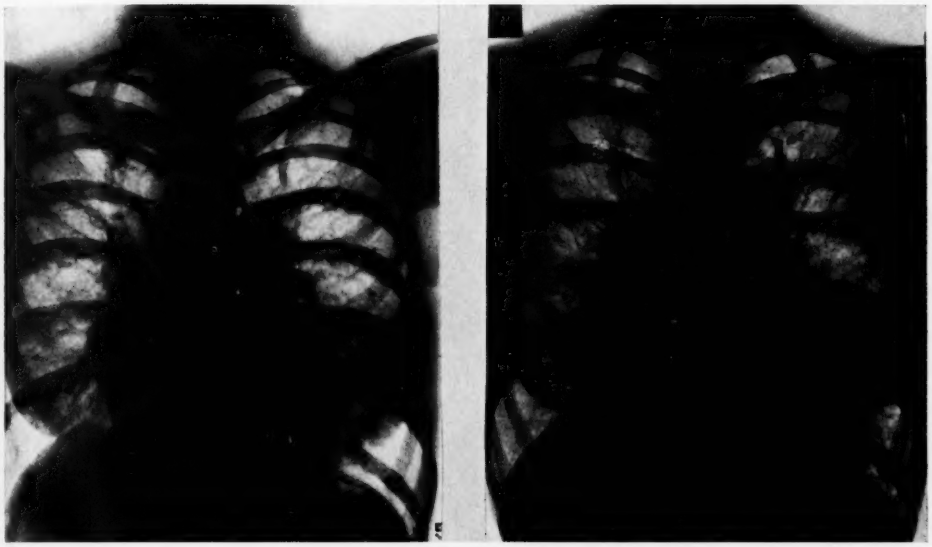


FIG. 3.—X-ray of Case 2. (A) 1954: showing evidence of old tubercle in right upper lobe and generalized cardiac enlargement, particularly of the left ventricle. Prominent arterial shadows in lungs. (B) 1956: showing increase in the size of the heart and the pulmonary artery.

June, 1956, he had a small hæmoptysis following sexual intercourse. Examination in April, 1957 showed a tall, well-built man. A prominent "a" wave could be seen in the venous pulse. The right radial pulse was regular and collapsing, the blood pressure being 180/60. Capillary pulsation was easily discernible. A sustained apex beat was palpable in the seventh left intercostal space in the anterior axillary line, and right ventricular pulsation could be felt to the left of the sternum. A systolic thrill was of greatest intensity in the fourth left intercostal space, and associated with this was a loud harsh systolic murmur heard best where the thrill was maximal but audible over the entire præcordium. A high-pitched, blowing, diastolic murmur commencing with the second sound was heard in all areas. The aortic second sound was loud; the pulmonary second sound could not be heard.

The Wasserman reaction was negative. The electrocardiogram showed right bundle-branch block (Fig. 1). X-ray examination showed enlargement of both right and left ventricles, with increased prominence of the main pulmonary artery and its branches (Fig. 4). In the light of our experience with the two previous cases, a clinical diagnosis of ventricular septal defect with pulmonary stenosis and aortic regurgitation was made.

At cardiac catheterization (Table I) a high "a" wave was recorded in the superior vena cava and right atrium. The pressure in the main pulmonary artery was raised (55/25), and the pulmonary artery wedge pressure was increased (23 mm. Hg). On withdrawal of the catheter into the right ventricle, a pulmonary infundibular stenosis was demonstrated, the systolic pressure in the main right ventricle being 130 mm. Hg. The increased oxygen content of blood samples from the pulmonary artery and high right ventricle indicated a shunt from left to right.

DISCUSSION

These three patients showed great similarity clinically, radiologically, and physiologically, and a composite description may be presented. However, it is appreciated that in the absence of confirmation by autopsy, our conception of the malformation is necessarily deductive.

All three patients gave a history of a cardiac murmur in infancy. Two were able to undertake normal activities in childhood and early adult life, but started to experience dyspnœa on exertion in their middle twenties: Case 2 thought that she had always been breathless on exertion, but

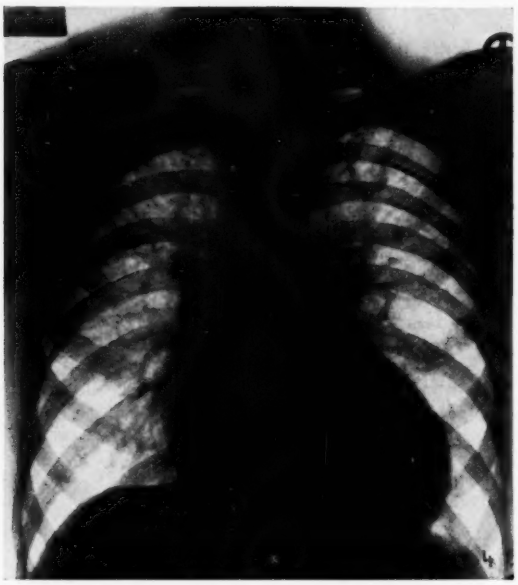


FIG. 4.—X-ray of Case 3. April, 1957: showing enlargement of the right and left ventricles with prominence of the pulmonary artery and its branches.

the breathlessness became much more severe at the age of 26. The collapsing pulse was a striking feature, and was confirmed by the blood pressure readings. The presence of a dominant "a" wave in the venous pulse, and signs of right ventricular hypertrophy, appear to be related to the severity of the pulmonary stenosis. A sustained apex beat suggesting enlargement of the left ventricle eventually became obvious in all three patients. A systolic thrill could be felt along the left border of the sternum, the exact site of its greatest intensity possibly depending upon the presence of either infundibular or valvular pulmonary stenosis. In one patient a diastolic thrill could also be felt. On auscultation both systolic and early diastolic murmurs were very loud. The intensity and length of these murmurs in Cases 1 and 2 led experienced observers to mistake the "to and fro" quality for the continuous murmur described by Gibson. The pulmonary second sound was very faint or could not be heard.

X-ray examination showed enlargement of both right and left ventricles with increase in the size of the branches of the pulmonary artery. The main pulmonary artery was also prominent in two of the patients. There was no apparent dextroposition of the aorta.

The electrocardiogram was not the same in the three patients. Case 1 and Case 2 eventually showed signs of deterioration of the left ventricle, but in Case 3 the right ventricle appeared to be predominantly affected, which can be explained by the much higher right ventricular pressure in this patient. The resultant pattern, therefore, seems to depend on the relative severity of the pulmonary stenosis and of the overloading of the left ventricle.

Cardiac catheterization demonstrated the presence of pulmonary stenosis, which was situated at the valve in one patient and in the infundibulum in the other two. Blood samples from the pulmonary artery were highly oxygenated and those from the right ventricle showed an unusually wide variation in oxygen content. The findings at operation have ruled out the existence of a patent ductus arteriosus in two cases, and in one of these the possibility of an aortico-pulmonary

defect was largely eliminated. In the light of these observations the shunt would appear to be due to a ventricular septal defect. Thus the withdrawal of occasional samples with a high oxygen content from the right ventricle is now interpreted as due to an inadequate mixing of the two streams of blood in this chamber, and not to the presence of pulmonary regurgitation.

There was no evidence of a shunt from right to left. Hence, despite the presence of pulmonary stenosis, the pulmonary blood flow exceeded the systemic flow in each case. Two patients showed the unusual combination of pulmonary stenosis with a raised pulmonary arterial pressure. This rise of pressure might be attributed to the effects, direct or indirect, of an increased flow. However, the high wedge pressure in Case 3 suggests that, at least in this patient, a raised left atrial pressure played some part in causing the pulmonary hypertension. Such a raised atrial pressure would imply a degree of failure of the left ventricle which is overloaded both by the aortic regurgitation and by the ventricular septal defect.

Since the first two patients were mistakenly thought to have a patent ductus arteriosus, it is relevant to consider the factors that gave rise to this erroneous diagnosis. The main difficulty was the murmur. This was in no case the typical murmur of a patent ductus, yet the intensity and duration of both systolic and diastolic elements were such as to suggest a continuous quality. The other cause of error was the collapsing pulse, which made a patent ductus arteriosus appear to be the more likely cause of the left-to-right shunt than a ventricular septal defect. Now that the presence of a patent ductus has been excluded, the collapsing pulse and the diastolic element of the murmur can with reasonable certainty be ascribed to aortic regurgitation.

It is pertinent to note that Soulié *et al.* (1949) experienced similar difficulties in distinguishing ventricular septal defect with aortic regurgitation from patent ductus arteriosus, as a result of misinterpreting the collapsing pulse, the murmur, and the findings at catheterization.

Summary

A description is given of three patients who appear to have ventricular septal defect with a left-to-right shunt, combined with pulmonary stenosis and aortic regurgitation. In two of these patients the shunt was erroneously thought to be through a patent ductus arteriosus, but this was disproved at operation. In the third patient the clinical and physiological features appeared to be sufficiently characteristic to establish the diagnosis without thoracotomy.

References

Abrahams, D. G., and Wood, P. (1951). *Brit. Heart. J.*, **13**, 519.
Breccia, G. (1906). *Gazetta degli Ospedali e delle Cliniche*, **27**, 625.
Bret, J. (1956). *Arch. Mal. Cœur.*, **49**, 1053.
Soulié, P., Routier, D., and Bernal, P. (1949). *Arch. Mal. Cœur.*, **42**, 765.

THE AORTIC SYSTOLIC MURMUR DEVELOPING WITH INCREASING AGE

BY

D. L. BRUNS * AND L. G. VAN DER HAUWAERT †

From the Department of Medicine, Postgraduate Medical School of London

Received October 21, 1957

For a number of years increasing attention has been paid to the evaluation of systolic murmurs (White, 1927; Fahr, 1930; Bass *et al.*, 1933; Shapiro, 1939; White *et al.*, 1942; Baker *et al.*, 1943; Levy *et al.*, 1943; Sodeman, 1944; and Master, 1948). It has been found that they are common in patients without evidence of cardiac disease, and the importance of considering factors other than organic valvular stenosis and regurgitation has been stressed (Levine, 1933; Freeman and Levine, 1933; Friedlander and Brown, 1935; Stewart, 1951). Phonocardiographic studies have helped to identify those due to aortic stenosis (Evans, 1947; Leatham, 1951; Mannheimer, 1955; Aravanis and Luisada, 1957; and Wells, 1957).

While clinicians are well aware of the high incidence of systolic murmurs in persons past middle age, only a few studies have been devoted to them. A number of investigators have appreciated that the aortic valvular deformities, sometimes responsible for these murmurs, were not necessarily due to rheumatic valvulitis (Broadbent and Broadbent, 1897; Dumas *et al.*, 1927; Friedberg and Sohval, 1939; Rednick, 1942; Evans, 1947). Others have emphasized the role of infundibular narrowing in the genesis of these murmurs (Gallavardin, 1924; Giraud and Bert, 1936).

The purpose of this paper is to give the incidence of aortic systolic murmurs, found in a hospital population aged 50 and over, and to analyse the clinical and pathological findings in such subjects.

Material and Methods

Three hundred patients over the age of 50 in the general medical wards of Hammersmith Hospital were examined (144 women and 156 men, average age 63·7 years). Well recognized valvular disorders of rheumatic, luetic, or congenital origin were excluded; but cases of ischæmic or hypertensive heart disease were included, if there was no evidence of severe congestive heart failure. Factors that may have modified the intensity of a murmur, such as hypertension, or anæmia, thyrotoxicosis or other high output states, were recorded. The patients could not be regarded as a sample representative of the healthy population of the same age, as most of them had a disabling illness and a number even some form of cardiovascular disease.

Special attention was paid to the pulse, blood pressure, the second heart sound, and the character of the murmur if present. The murmurs were classified into grades (Levine, 1933). To avoid any possible error, patients with very faint (grade 1) murmurs were included in the group without murmurs. Phonocardiographic tracings from the aortic and mitral areas were made in representative cases. Twenty-three of these 300 patients came to autopsy.

Concurrently a pathological examination was made of the heart in 168 subjects (male, 95, and female, 73) reaching necropsy during the present study, excluding the same valvular disorders as in the clinical analysis. As well as the routine examination, special attention was paid to the

* Fellow of the U.S. National Foundation for Infantile Paralysis.
† British Council Scholar.

presence or absence of thickening of the aortic valve, especially in the central part of the base of each cusp. If the cusps could be pressed flat against the aortic wall without any protuberance, the valve was recorded as normal. The valve thickening was considered slight, with a protuberance up to 3 mm., moderate 3–5 mm., and great over 5 mm. Representative microscopic sections were made in selected cases. Dilatation of the aorta was recorded by measuring with a ruler the widest diameter of the ascending aorta and comparing it with the diameter of the aortic ring before fixation.

Results

Clinical Study. Systolic murmurs were heard in 146 of the 300 cases studied. The incidence by decades is shown in Table I. The majority were best heard over the second right intercostal space but also in a band down the sternum, out towards the apex. The murmur was confined to the aortic area in 14 cases and to the apex in 22. In the remaining 110 cases the murmur was heard in both areas, being loudest at the apex in 43, at the aortic area in 39, and of equal intensity in both areas in 28; 112 murmurs were of slight intensity (grade 2), and 34 were moderate to loud (grade 3 or over). The latter were often transmitted into the neck. A thrill was felt over the aortic area in only three cases. One loud murmur in the aortic area was musical. In nine cases, where there was a hyperkinetic circulation, a loud systolic murmur was well heard over the whole præcordium, including the pulmonary area, while in all the other patients the murmur was diminished in the latter area. The murmurs tended to be short, leaving an appreciable gap before the second heart sound. In only three cases was a soft pan-systolic murmur heard at the apex. Two of these patients had a recent myocardial infarction and one had severe hypertension. In addition, in one hypertensive patient an early diastolic murmur was heard at the left sternal border.

The second heart sound at the aortic area was loud in most patients, although normal in some others. Where splitting of the second heart sound was heard, it was not abnormally wide, except in the few patients with bundle-branch block.

Forty out of the 112 patients with a grade 2 murmur and 18 out of 34 with a murmur of grade 3 or over, had associated hypertension, anæmia (hæmoglobin 10 g. or less), thyrotoxicosis, or liver failure due to cirrhosis.

TABLE I

Incidence of Murmurs in Relation to Age

Age group	Patients studied	Number with murmurs	Grade 2	Grade 3 or over
50–59	115	43 (37%)	39	4
60–69	102	48 (47%)	36	12
70–79	70	46 (66%)	32	14
80–89	13	9 (69%)	5	4
Total ..	300	146 (49%)	112 (37%)	34 (11%)

Phonocardiography

Thirty-three phonocardiographic tracings were made from representative patients in different age groups and ætiological categories.

One case of recent myocardial infarction, mentioned previously, showed a soft pan-systolic murmur at the apex and a short ejection murmur at the aortic area. In 26 cases a "spindle"- or "diamond"-shaped murmur was shown, depending on the loudness (Fig. 1, 2, and 3). The point of maximal intensity, as measured over at least four cycles, coincided with the middle of systole in two cases (No. 4 and 25, on Fig. 1) and fell earlier in all the others. In seven cases, in which this pattern was not found, the murmur occupied the first half or two-thirds of systole. Hence, in all cases the clinical impression was confirmed that the murmur was short, relatively early in systole,

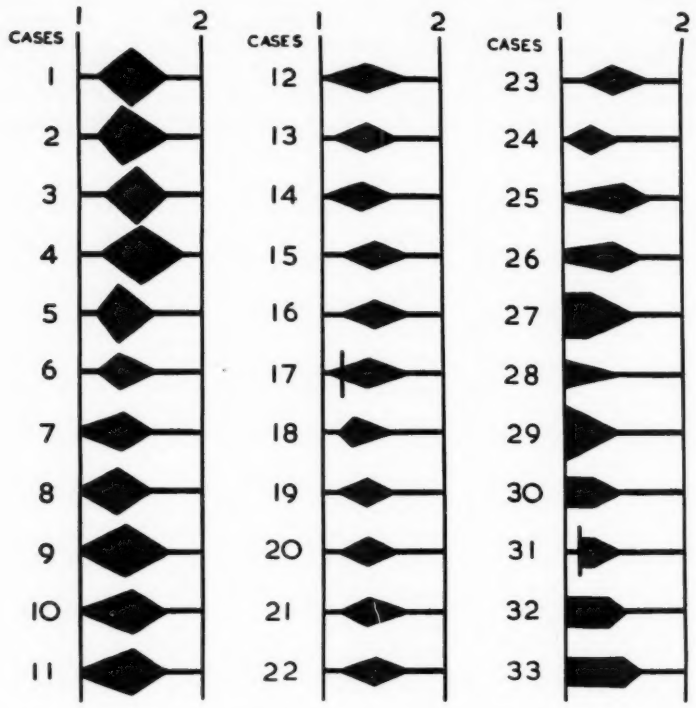


FIG. 1.—Diagrammatic representation of the systolic murmurs recorded in 33 patients over the age of 50 without evidence of aortic stenosis. The vertical line in Cases 17 and 31 represent a systolic click.

and ended an appreciable time before the second sound, which was often accentuated. No la systolic murmurs were recorded. The pattern of the murmur at the apex was indistinguishab from that at the aortic area, when it was audible in both positions. In 9 out of 10 cases, inhal tion of amyl nitrite caused an intensification of the murmur without changing its position in systol The murmur in hypertension and in hyperkinetic states was similar in all respects to those describe In three cases of atrial fibrillation the loudness of the murmurs varied with the duration of the pr ceding diastolic interval. On two occasions an early systolic click was recorded: the inhalation amyl nitrite increased the intensity of the systolic click and shortened the interval between it an the first sound (Fig. 4).

Pathology. Some thickening of the cusps of the aortic valve was found in 120 of the 168 subjec coming to necropsy (of whom 23 were examined by the authors and included in the clinical study This thickening appeared to originate in the aortic aspect of the base of the cusp (Fig. 5), so th the latter was less mobile and projected into the aortic lumen. In mild cases the thickening appeare to be fibrous and was confined to the central region of the cusp. With increasing severity, it sprea towards the free margin and there was associated calcification (Fig. 6). In all cases the free marg of the valve was mobile and unaffected by this process. Fusion of the commissures was not see slight adhesions over a distance of 1 to 2 mm. did not seem important, as they were just as freque in normal valves without any thickening. Histological examination (Fig. 7) showed, in cas recorded as slight, some fibrous thickening in the proximal sixth of the fibrous lamina and

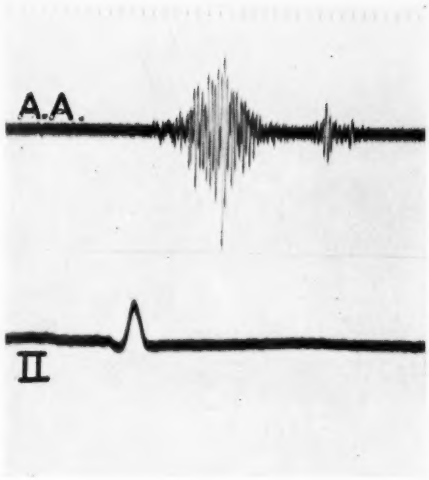


FIG. 2.—Diamond-shaped systolic murmur in the aortic area (A.A.) from a patient aged 67.

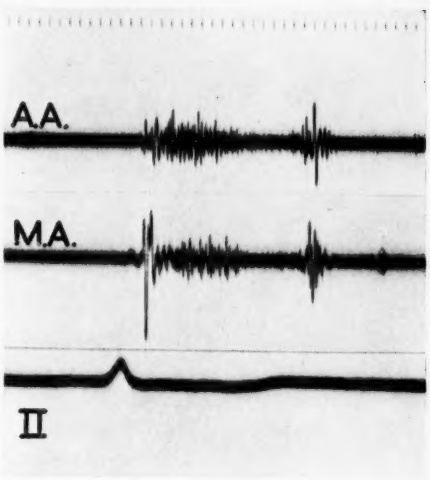
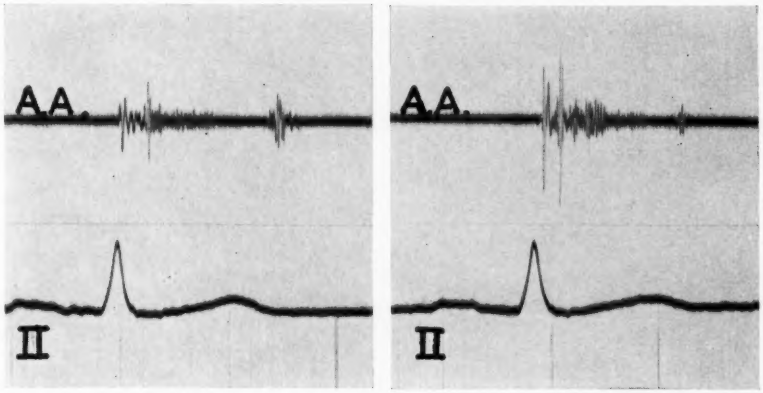


FIG. 3.—Spindle-shaped systolic murmur heard at the aortic and mitral area (A.A. and M.A.).

Time scale: One division = 0·02 sec. in Fig. 2 and 3.



A B

FIG. 4.—Systolic click and murmur in the aortic area, (A) before and (B) after inhalation of amyl nitrite.

the pocket at the point of attachment of the cusps. Moderate thickening was characterized by calcification within the fibrous lamina at the root of the cusps, with accompanying slight fibrous thickening, and great thickening by gross nodular calcification at the point of attachment of the cusps and the adjacent part of the fibrous lamina. Although the base of the valve projected into the aortic lumen, in no case was there severe obstruction to the passage of blood and the circumference of the most affected valve was still 6 cm., which is only slightly less than the normal figure of 7 to 8 cm. Figure 8 shows the relationship of this valve thickening to the age group, where there is a tendency for it to become more apparent with increasing years. The pulmonary valves remained entirely free from similar alterations throughout all the age-groups.

The ratio of the widest diameter of the ascending aorta to the diameter of the aortic ring

FIG. 5.—Diagrammatic representation of the aortic valve, showing the position and the mode of progression of the fibrous thickening and secondary calcification.

FIG. 6.—Calcified atheromatous nodules at the base of the valve, the leaflets of which are held open by a rubber tube.

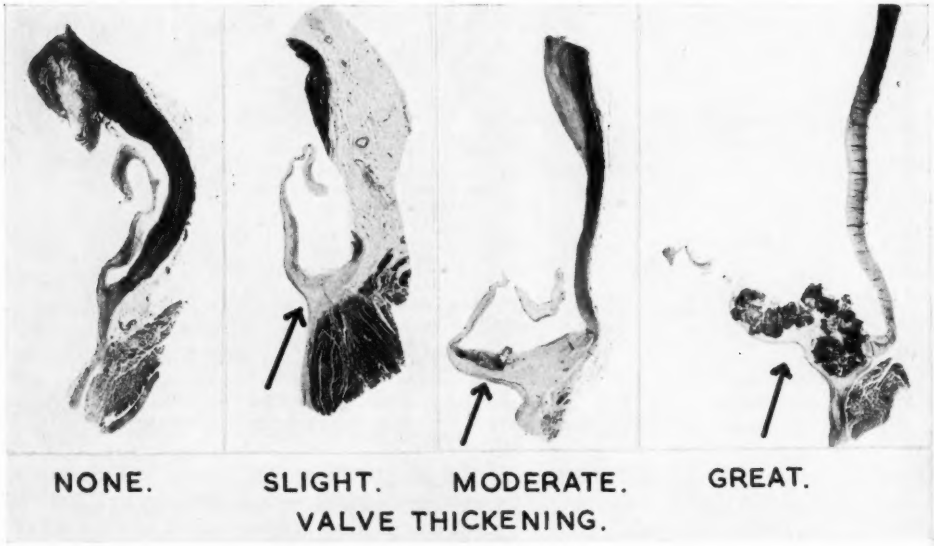


FIG. 7.—Histological sections of the aortic valve, showing different degrees of thickening at the base of the cusp.

increased from 0·94 (0·80 to 1·2), in 35 cases under 50 years of age, to 1·14 (0·93 to 1·4) in 100 cas older than this. Aneurysmal dilatation of the ascending aorta was not seen. We have intentiona avoided further statistical analysis of these data, as our simple method of measurement of t diameters would not permit any detailed conclusions.

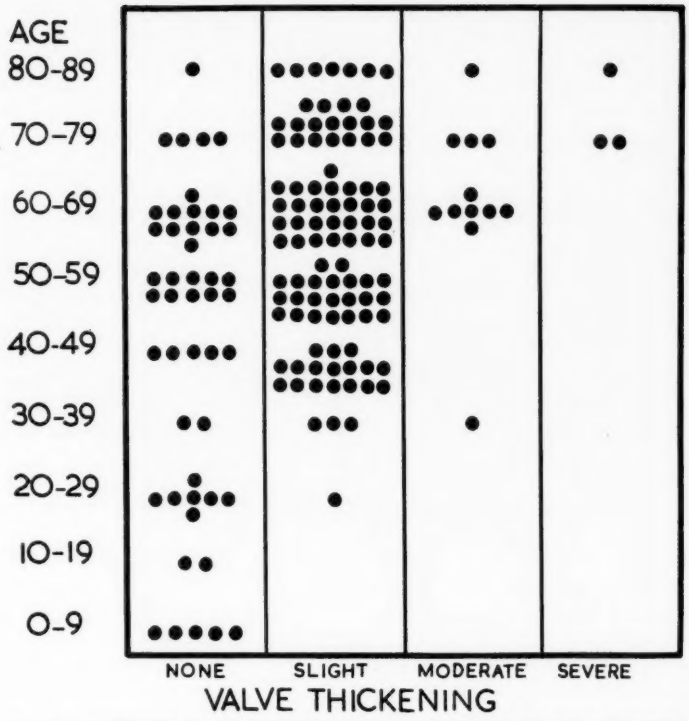


FIG. 8.—The relationship between the degree of valve thickening at necropsy and the age.

TABLE II

CORRELATION BETWEEN THE CLINICAL AND PATHOLOGICAL FINDINGS IN 18 CASES WITHOUT HYPERKINETIC CIRCULATION

Intensity of the murmur	Valve thickenings			
	None	Slight	Moderate	Great
None	4	6	1	—
Grade 2	—	4	1	—
Grade 3 or over	—	—	—	2

Correlation between clinical and pathological findings. Twenty-three patients, who had been studied in life by the authors, came to autopsy. As shown in Table II, there is a relationship between the intensity of the murmur and the degree of thickening of the aortic valve leaflets in 18 patients, who did not have a hyperkinetic circulation. Of the five cases with a hyperkinetic circulation, four had slight valve thickening, two of whom had a grade 2, and two a grade 3 murmur.

DISCUSSION

In contrast to childhood, where the right ventricular outflow tract seems to be the site of origin of most physiological murmurs (Bass *et al.*, 1933; Friedlander and Brown, 1935; Sodeman, 1944; Mannheimer, 1955), the present study points towards the aortic valve as the origin of the great majority of murmurs heard in people over the age of 50 years.

It must be emphasized that this series represents a general hospital population, in whom there were many patients with hypertension or with a hyperkinetic circulation. Therefore, it is likely that the incidence of these murmurs in the general population is less.

The pathological finding of thickening and even calcification of the base of the aortic valve leaflets is so common at necropsy, in the age groups over 50, that one is inclined to consider at least the more advanced degrees as the explanation of an aortic systolic murmur with increasing age. These pathological changes are different from those of rheumatic origin in that the latter tend to be localized more in the free edges of the valves with associated distortion and fusion of the cusps. Since the original description by Mönckeberg (1904) others have confirmed that the incidence of calcification beginning in the base of the aortic valve leaflets is high and that many of these changes may be of atherosclerotic character (Sohval and Gross, 1936; Lesnick and Schlesinger, 1938; Hultgren, 1948; Boas *et al.*, 1954). These authors, however, were mainly interested in the severe degrees of calcification leading to true calcific stenosis and did not stress the importance of considering lesser degrees of valvular changes in the production of murmurs in elderly people.

It appears from the present study that sclerotic lesions of old age, unless very advanced, do not usually produce a significant hæmodynamic obstruction and therefore tend to be benign, although they can cause a loud murmur. It is important to recognize the benign nature of such a murmur and not to label the patient as having serious heart disease, but rather to consider it as part of the natural ageing process. The murmur is exaggerated by increased speed of ejection through the slightly narrowed orifice and one would therefore expect it to be louder when the output of the heart is high, as in anæmia or thyrotoxicosis.

Clinically, the murmur of aortic valve sclerosis, when heard at the apex, may be differentiated from that due to mitral regurgitation, by its audibility in the aortic area, its transmission into the neck, its limitation to early or mid-systole, and its intensification by inhalation of amyl nitrite (Barlow and Shillingford, 1938). Differentiation has to be made from rheumatic aortic stenosis: the absence of a past history of heart disease and of other associated valvular lesions decreases the likelihood of a rheumatic origin in this age group. Furthermore, signs associated with obstructive aortic stenosis are nearly always lacking, such as left ventricular hypertrophy, alterations in the form of the pulse, and paradoxical splitting of the second sound. Phonocardiography showed that, while many rhomboid-shaped murmurs, similar to those seen in aortic stenosis (Leatham, 1951), were present, there was a significant difference, in that the point of maximal intensity fell almost invariably in the first half of systole. This is in agreement with the recent findings of Aravanis and Luisada (1957) who stated that 87 per cent of the murmurs in "relative aortic stenosis" were early diamond-shaped, whereas 67 per cent of cases with obstructing stenosis were late diamond-shaped. On the other hand, if one accepts the view that not all cases of aortic stenosis are rheumatic in origin, but that some of them are due to an arteriosclerotic process gradually developing from valve sclerosis to true obstruction, one should not be surprised to find borderline cases.

Summary

The incidence of systolic murmurs has been studied in 300 hospital patients over the age of 50.

Clinical and phonocardiographic studies have shown that the majority arise in the aortic valve.

Aortic systolic murmurs become more frequent with increasing age: they can be loud especially in the presence of a hyperkinetic circulation.

The responsible pathological lesion in many cases appears to be the thickening of the base of the aortic valve cusps, which produces a murmur but does not obstruct significantly the outflow.

Addendum on the Mode of Production of Murmurs of Aortic Sclerosis

We were reluctant to accept these minor changes in the base of the aortic valve as a cause of the murmurs. Therefore we set up a series of tests in a model circulation, resembling the experiments of Bondi (1936).

He described murmurs (audible eddies) produced in a continuously flowing stream of water, by various shapes of glass or brass tubes, at varying rates of flow. He did not study sounds produced by pulsatile flow. In view of the obvious importance of the pulsatile factor the Melrose artificial heart-lung machine was used in these experiments.

Brass tubes with varying types of narrowed lumen were placed in the outflow of the pump with the phonocardiograph-microphone 2 cm. distal to the obstruction. The loudest murmurs were always obtained with tubes having an abrupt protrusion into their lumina. Figure 9 shows the type and intensity of murmurs recorded with a tapered narrowing and with an identical degree of narrowing produced by a diaphragm. In both cases the murmur is typically rhomboid-shaped but the diaphragm causes greater loudness and intensity for the same stroke-output. The ratio (0·125) of the protrusion to the lumen, in this example, is the same as that of a moderate pathological valve thickening (3 mm.) to the diameter of the aortic ring (24 mm.).

Thus even a slight but abrupt protuberance is capable of producing a murmur of considerable intensity, while a gradually changing diameter (such as dilatation of the ascending aorta) is less likely to produce an audible sound.

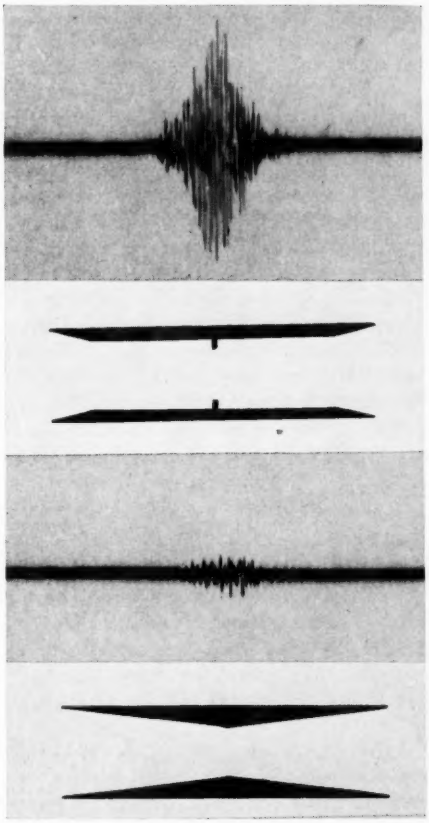


FIG. 9.—Murmurs recorded in model experiments by two brass tubes (seen in cross-section) with the same degree of stenosis but different internal configuration. The stroke-output of the pump and the sensitivity of the phonocardiograph were the same.

We would like to express our thanks to Professor McMichael and Dr. Shillingford for the great interest they hav shown in this study and for advice and assistance in the preparation of this paper. We also wish to thank Mr. C Lordan for technical help.

REFERENCES

Aravanis, C., and Luisada, A. A. (1957). *Amer. Heart J.*, **54**, 32.
Baker, L. A., Sprague, H. B., and White, P. D. (1943). *Amer. J. med. Sci.*, **206**, 31.
Barlow, J. B., and Shillingford, J. (1958). *Brit. Heart J.*, **20**, 162.
Bass, M. H., Mond, H., Messeloff, C. R., and Oppenheimer, E. T. (1933). *J. Amer. med. Ass.*, **101**, 17.
Boas, E. P., Elster, S. K., and Adlersberg, D. (1954). *Amer. Heart J.*, **48**, 485.
Bondi, S. (1936). *Ergebn. d. inn. Med.*, **50**, 308.
Broadbent, W. H., and Broadbent, J. F. H. (1897). *Heart Disease*. Baillière, Tindall, & Cox, London.
Dumas, A., Brunat, and Vernaud (1927). *Lyon Méd.*, **140**, 23.
Evans, W. (1947). *Brit. Heart J.*, **9**, 1 and 225.
Fahr, G. (1930). *Nebraska med. J.*, **15**, 458.
Freeman, A. R., and Levine, S. A. (1933). *Ann. intern. Med.*, **6**, 1371.
Friedberg, L. K., and Sohval, A. R. (1939). *Amer. Heart J.*, **17**, 452.
Friedlander, R. D., and Brown, M. G. (1935). *Ann. intern. Med.*, **8**, 893.
Gallavardin, M. L. (1924). *Lyon Méd.*, **133**, 33.
Giraud, G., and Bert, J. M. (1936). *Arch. Mal. Cœur*, **29**, 613.
Hultgren, H. N. (1948). *Arch. Path.*, **45**, 694.
Leatham, A. (1951). *Brit. Heart J.*, **13**, 153.
Lesnick, G., and Schlesinger, M. J. (1938). *Amer. Heart J.*, **16**, 43.
Levine, S. A. (1933). *J. Amer. med. Ass.*, **101**, 436.
Levy, R. L., Stroud, W. D., and White, P. D. (1943). *J. Amer. med. Ass.*, **123**, 937.
Mannheimer, E. (1955). *Adv. Pediatr.*, **7**, 171.
Master, A. M. (1948). *Arch. intern. Med.*, **81**, 518.
Mönckeberg, J. G. (1904). *Virch. Arch. pathol. Anat. Physiol. Klin. Med.*, **172**, 472.
Rednick, M. S. (1942). *Ann. intern. Med.*, **16**, 1197.
Shapiro, M. J. (1939). *Amer. Heart J.*, **17**, 416.
Sodeman, W. A. (1944). *Amer. J. med. Sci.*, **208**, 106.
Sohval, A. R., and Gross, L. (1936). *Arch. Path.*, **22**, 477.
Stewart, I. M'D. G. (1951). *Brit. Heart J.*, **13**, 561.
Wells, B. G. (1957). *Brit. Heart J.*, **19**, 129.
White, P. D. (1927). *Amer. J. med. Sci.*, **174**, 731.
——, Adams, F. D., and Craib, D. (1942). *Amer. J. med. Sci.*, **203**, 52.

VENTRICULAR SEPTAL DEFECT WITH PULMONARY STENOSIS

BY

L. BROTMACHER AND MAURICE CAMPBELL

From the Cardiac Department, Guy's Hospital, and the Institute of Cardiology

Received October 21, 1957

About one-tenth of our patients with an atrial or ventricular septal defect who have had cardiac catheterization had pulmonary stenosis as well. Wood (1956) found much the same. This proportion is probably higher than the true incidence, for patients with the double lesion are more likely to be catheterized, but the association is common enough to be of some practical importance from the point of view of diagnosis and surgical treatment. It is found much more commonly than would be expected by chance, though this is not surprising in the case of ventricular septal defects at least, for the two abnormalities always occur together in Fallot's tetralogy.

We are describing 15 acyanotic patients in whom a ventricular septal defect with a left-to-right shunt of moderate size was associated with pulmonary stenosis. These 15 had a systolic gradient between the right ventricle and the pulmonary trunk of between 35 mm. and 100 mm. Hg. We think that 35 mm. is about the level where there is likely to be an organic stenosis, and it was also the smallest systolic gradient that we have seen in a patient with proven pulmonary stenosis (by necropsy in Case 78). During the same period we have made a clinical diagnosis of uncomplicated ventricular septal defect in about 175 patients, of simple pulmonary stenosis in about 150, and of Fallot's tetralogy in about 700. The true proportion of patients with Fallot's tetralogy is, however, much less than this for a large number of these have been sent to us specially for consideration of surgical treatment. We are also discussing briefly eight other patients with a gradient of between 15 and 31 mm. between the right ventricle and the pulmonary artery. Sometimes, we think this is due to a Venturi effect, but its significance is discussed later.

Clinical Features

Diagnosis. Severe pulmonary stenosis and large ventricular septal defects are easy to diagnose when occurring alone, but lesser degrees may be difficult, especially if both lesions are present together. If radioscopy confirms a left-to-right shunt in such a patient, the diagnosis of ventricular septal defect alone may be accepted, as happened several times in our series. The double diagnosis was made clinically in only one of these patients (Case 74). This contrasts with cases of atrial septal defect with pulmonary stenosis where both were often recognized: presumably the rougher systolic murmur when the defect is ventricular makes the double diagnosis more difficult on auscultatory signs alone.

The diagnosis thought most likely at first was ventricular septal defect in seven (including one with pulmonary regurgitation), pulmonary stenosis in three, and both conditions in one patient. In the remaining four the presence of basal diastolic murmurs suggested the possibility of persistent ductus arteriosus alone or with a septal defect: necropsy confirmed that this was present as well as the other two conditions in Case 71; the long murmur in diastole was heard soon after the patient had recovered from subacute bacterial endocarditis and later disappeared in Case 67; and the cause of the murmur remains unknown in the other two. The diagnosis of ventricular septal defect and pulmonary stenosis was confirmed at operation in one and at necropsy in two patients.

In retrospect, the combined diagnosis could have been made more often than it was, especiall in those with moderately severe pulmonary stenosis. In patients with clinical and radiologica evidence of ventricular septal defect and without auscultatory evidence of pulmonary hypertensio right ventricular preponderance in the electrocardiogram suggests the presence of associated pu monary stenosis. Ten of the 15 patients showed right ventricular preponderance, two of thes having T inversion in V1 and V2 and four others in V1 only; three probably had some right pre ponderance, but two did not have any evidence of this. There may be evidence of some hypertroph of both ventricles in many cases of ventricular septal defect, but right ventricular *preponderance* uncommon unless there is fairly severe pulmonary hypertension (Mannheimer *et al.*, 1957).

Symptoms and General Features. These 15 patients do not seem to form a homogeneous grou and though apart from our notes we have a clear picture of ten of them, it is not easy to mak many generalizations. They were clinically acyanotic when they were first seen, and as a rule n greatly disabled. Our oldest patient is, however, only 25 years old. In spite of this, we think tha for two patients with ventricular septal defects of the same size, the outlook is better for the on with moderate pulmonary stenosis in addition; since the evidence of this tending to become mo severe is inconclusive, whereas the pulmonary arteriolar resistance associated with large shun tends to rise (Brotmacher and Campbell, 1958).

All 15 patients were clinically acyanotic at rest when the diagnosis was first made, but even the there was a small right-to-left shunt in two (Cases 66 and 77). One became cyanotic on exerci and two others may have done so (Cases 73, 76, and 79). Three of the four who were recatheterize from two to seven years later had this done because they had become cyanotic: in two the arteri oxygen saturation at rest had fallen (Cases 74 and 80) and in the third it fell on exertion (Case 67 Another patient was always acyanotic when she was 3 but became cyanotic on exertion when sh was 7 years old (Case 71). This means that of the 15 patients, 2 were slightly cyanotic at rest an 5 others became so after exercise by the time they last attended hospital.

Squatting was recorded in one patient only when he was first seen: he may have become cyanot on exertion, for two years later he had become so, even at rest (Case 74). Two others start squatting later as they became cyanotic (Cases 67 and 71). Three had severe kyphoscoliosis and one of these it was an important part of her disability (Case 77).

The size of the heart was variable, the enlargement being slight (c.t.r. 50–54%) in five, modera (c.t.r. 55–59%) in five, and great (c.t.r. over 60%) in five cases—not very different from our findin in uncomplicated ventricular septal defect. Those with only slight enlargement had the smal shunts, an average of 2·4 against 4·4 litres a minute in the others, but there was so much overlappi that this is unlikely to be the whole explanation of the differences in the size of the heart. Bo ventricles usually seemed to be enlarged but this often happens with ventricular septal defect alo The aortic arch was left-sided in 14 patients, but right-sided in the fifteenth.

Patients who have Died. Two of these patients have died, one after an attempt to close l ventricular septal defect and one with other congenital abnormalities and congestive heart failu Short case reports follow.

Case 71. A girl, aged 3 when she was first seen, was acyanotic and had a very large heart: she w thought to have a septal defect. Later she became more disabled and cyanotic on exertion, and star squatting: a continuous murmur was then heard and a persistent ductus suspected. When she was catheterization showed pulmonary stenosis and confirmed a left-to-right shunt, and the catheter pas from the right ventricle to the aorta. As she was becoming worse, the co-existing ductus was closed and attempt was made to close her ventricular septal defect, but unfortunately she died.

At *necropsy* the heart was greatly enlarged and there was nothing to distinguish it from a heart w Fallot's tetralogy and a persistent ductus that had been successfully closed. The attempts to close ventricular septal defect, which was at the usual high site but unusually difficult to approach, and to reli the infundibular stenosis had not been successful but prevented study of the original anatomy. Th were no other congenital abnormalities.

Case 78. A boy, aged 16, did not play games, but complained of little and cycled up to 50 miles i day. He was acyanotic but had an enormous heart (c.t.r. 78%). Catheterization demonstrated a left-

right shunt of 8·2 litres a minute and an infundibular stenosis with a gradient of 35 mm. Hg. When 19 he came into hospital again, this time with congestive heart failure, from which he died.

At *necropsy* the heart weighed 980 g.—a size that was not easily explained by the lesions that were found, but the coronary arteries were very small. There was a ventricular septal defect, 2·5 cm. across, at the usual site. There was infundibular stenosis with an opening 1·5 cm. in diameter and a large infundibular chamber. The pulmonary valve was bicuspid but not stenosed. The aorta seemed to over-ride the ventricular septal defect and was small. At the level of the ligamentum arteriosum it became smaller but unlike an ordinary coarctation, it was also hypoplastic beyond this; there was general medio-necrosis cystica of the aorta and pulmonary artery. There were many congenital abnormalities outside the heart, the most striking being an additional bronchus to the right upper lobe, two left renal arteries, but an absence of the right adrenal gland and right kidney and ureter. This case will be reported fully by Baylis.

Hæmodynamic Findings

The diagnosis was proved at cardiac catheterization and the pulmonary artery was intubated in every patient. The aorta was entered from the right ventricle in four. In all there was proof of a left-to-right shunt, but the shunts were small for cases of ventricular septal defect, averaging 3·2 litres a minute. There was no tendency for the shunts to change in size with age or, with the exception of Case 78, to depend on the size of the pulmonary gradient. This exception was the boy who died, who had the lowest gradient of 35 mm. and the largest shunt, 8·2 litres: he was the only patient where it was more than 5·2 litres a minute. The data are given in Table I.

TABLE I

Hæmodynamic Data in Patients with Ventricular Septal Defect and Pulmonary Stenosis

Case No.	Sex and age	Surface area (sq. m.)	Systemic flow (l./min.)	Pulm. flow (l./min.)	Art. O_2 sat.	Pressures (mm. Hg)					
						Systemic	Right ventricle		Pulmonary artery		Pulm. cap. (mean)
							Body	Infundibulum (if lower)	Phasic	Mean	
66*	M5	0·91	2·9[2]	6·1[2]	93	110/75[3]	74/0	37/0	36/16	25	—
67*	M6	0·68	2·2	3·7	95	110/75[3]	89/4	—	35–57/8–21	—	—
	M13	1·09	5·2	6·0	95	95/65	89/2	19/3	13/4	—	3
68	F7	0·86	4·0	9·2	99	150/110†	98/1	42/9	48/33	41	12
69	F7	1·00	5·2	6·2	95	90/34	88/0	22/2	23/10	14	6
70	F7	0·70	8·9	14·1	96	76/52	64/3	31/7	26/9	16	8
71	F7	0·84	2·9	5·3	97	88/55	86/8	30/8	21/9	14	12
72	F9	1·00	3·0	6·0	95	120/80[3]	92/6	—	19/14	17	13
73	F5	0·65	—	—	94	105/75[3]	114/9	—	—	—	—
	F11	1·10	6·8	11·2	95	110/85[3]	110/5	13/8	16/4	11	7
74	M10	1·26	—	—	98	120/75	100/0	—	—	—	—
	M12	1·50	3·5[1]	5·1[1]	89	130/85	95/9	28/6	15/3	8	0
75	F13	1·42	7·1	10·6	95	104/70	104/2	37/2	16/4	7	3
76*	M14	1·11	4·9	8·1	95	125/81	110/0	—	23/8	11	—
77	F15	—	2·6[2]	5·2[2]	91	115/80	78/0	—	18/9	13	9
78*	M17	1·37	4·5	12·7	97	106/61	85/2	51/4	50/15	30	—
79*	F19	1·56	5·4	9·5	95	102/72	98/5	—	30/7	24	—
80*	M25	1·75	4·4	6·5	94	102/67	121/3	31/2	22/10	16	—
	M26	1·73	4·5	6·4	90	120/80[3]	104/15	39/8	27/12	19	—

[1] Veno-arterial shunt of 0·7 l./min. present. [2] Veno-arterial shunt possibly present.
[3] Not measured during cardiac catheterization. † Generally 110/70.
* These six were included in Table IX by Campbell (1954) as Cases B1–5 and E2.

Excluding patients with a high pulmonary arteriolar resistance that had reduced the shunt, Brotmacher and Campbell (1958) found that the average left-to-right shunt in uncomplicated

ventricular septal defect was 8·8 litres a minute, so that in the present 15 patients it was compara tively small. In fact, pulmonary stenosis reduced the average shunt to about the same level as di a pulmonary arteriolar resistance of between 6 and 12 units (3·2 and 3·5 litres a minute respectively)

In three patients the oxygen content of the pulmonary arterial blood was more than 1·0 m per 100 ml. above that of the right ventricle, suggesting that part of the shunt was directly into th pulmonary artery. In none of these three was there any clinical evidence to suggest a persisten ductus, and in one it was excluded at necropsy. No pulmonary arterial sample was obtained i the patient in whom the presence of a persistent ductus was confirmed at necropsy.

The systolic gradient between the right ventricle and the pulmonary trunk was between 35 an 52 mm. in five and between 60 and 99 mm. in eleven patients, counting Case 67 twice sinc the gradient had risen from 43 to 76 mm. during seven years. The site of the gradient wa demonstrated in thirteen patients—at infundibular level in nine (four of whom had gradient of less than 10 mm. at valve level also), at valve level in two, and at both levels, though mainl infundibular, in two (Cases 74 and 75). This distribution might be found in a group with Fallot' tetralogy though generally there would be more at the valve level and more at both levels. It con trasts sharply with cases of atrial septal defect and pulmonary stenosis where it is nearly always a valve level.

The systolic pressure in the right ventricle was high in all these 15 patients, and was withi 20 mm. of the systemic level in all but five of them. The pulmonary arterial systolic pressure wa moderately increased in two (48 and 50 mm., Cases 68 and 78), slightly above normal in two (in on of whom it had fallen to normal seven years later, Case 67), and normal in the remainder. In thos where the pressure was raised, the stenosis cannot have obstructed the pulmonary flow greatly, bu presumably the pressure would have been still higher if there had been no stenosis. The pulmonar arterial tracings showed well-defined pulsations, whereas in Fallot's tetralogy it is not often possibl to record much more than a mean pressure. The pulmonary arterial samples were less saturate than the ventricular in two patients only, though this is common in Fallot's tetralogy when th catheter obstructs appreciably the flow through the stenosis. The mean pulmonary capillar venous pressure was 8 mm., which is 1 mm. less than the mean of the patients with a ventricula septal defect and a normal pulmonary arterial pressure.

Recatheterization after an Interval. Catheterization was repeated in four patients but in tw it had not been possible to enter the pulmonary artery on the first occasions. In both these th systolic pressure in the right ventricle was about the same, and not much below the systemic (Cases 7 and 74).

In Case 80 the interval was only two years because he had become slightly cyanosed and wa able to do rather less: the findings were hardly changed except that the arterial oxygen saturatio had fallen from 94 to 90 per cent. It had fallen in one other (Case 74, 98 to 89%) but was u changed in two (Cases 67 and 73). Case 67, however, was always acyanotic when 6, but whe 13 became cyanotic on exertion and this was confirmed during the second catheterization (art. O sat. 95 to 90% with exercise). The right ventricular pressure was unchanged (89/2–4) but th pulmonary arterial pressure which had been variable earlier (57/21 and 35/8) was now lower. Th left-to-right shunt was reduced and, relatively, greatly reduced, from 2·1 to 0·7 litres/sq. m./min.

Patients with Smaller Gradients

We are discussing more briefly 8 patients who had a ventricular septal defect with a left-to-rig shunt and a systolic gradient between the right ventricle and pulmonary trunk of from 16 to 31 m (see Table II). The gradient was demonstrated on a withdrawal tracing in 5 of these 8, and w at infundibular level in two and at valve level in three. In two the catheter passed through th defect to the left ventricle, which is unusual with cases of ventricular septal defect.

In three of them there was some evidence against the presence of any organic stenosis. one, with a gradient of 20 mm., no obstruction could be demonstrated at necropsy (Case 1, Bay

et al., 1955), although a functional infundibular stenosis may have been present in life (Case 60). In the second, with a gradient of 16 mm., a loop of catheter could be passed into the pulmonary artery (Case 59). These two had very large hearts and aortic regurgitation and both had pulmonary flows of over 14 litres a minute, and the gradient recorded may have been due to a Venturi effect. In the third, changing conditions may explain the gradient of 18 mm. for the recorded infundibular pressure was higher than that recorded in the body of the right ventricle (Case 65).

In the remaining five, it is more difficult to decide whether they had a small organic stenosis or not. In two the gradients (16 and 18 mm.) were no larger than in those just described but in the other three they were between 23 and 31 mm. Two had a large pulmonary flow and the pulmonary arterial systolic complexes were notched, suggesting that here too the pulmonary pressure as recorded was reduced as the result of a Venturi effect. There may, however, have been a slight stenosis in some of them, and the possibility of this is greater where the pulmonary flow was only moderately raised; or the obstruction may have been relative, a normal-sized valve ring intervening between a dilated outflow tract and a dilated pulmonary trunk.

TABLE II

HÆMODYNAMIC DATA IN PATIENTS WITH VENTRICULAR SEPTAL DEFECT AND A SMALL RIGHT VENTRICULAR TO PULMONARY ARTERY PRESSURE GRADIENT

Case No.	Sex and age	Surface area (sq. m.)	Systemic flow (l./min.)	Pulm. flow (l./min.)	Pressures (mm. Hg)					
					Systemic	R. V.		P. A.		Pulm. cap. (mean)
						Body	Infundibulum	Phasic	Mean	
58	F4	0·62	3·2	10·2	129/76	62/14	—	46/18	[2]32)	15
59	M7	0·84	4·1	14·4	100/50[2]	53/5	—	37/20	[2]27)	—
60	M9	0·94	4·5	14·2	140/50	75/0	55/2	55/25	(35)	—
61	M10	1·08	4·3[1]	8·7[1]	80/50	76/9	—	58/32	(42)	—
62	F11	—	Left-to-right shunt present		110/70	43/8	—	18/10	(13)	—
63	F12	1·67	9·4	15·4	126/71	47/9	—	24/9	(16)	12
64	F18	1·62	4·5	21·2	85/4 (L.V.)	42/0	—	11/2	(6)	3
65	F19	1·52	3·5	8·2	130/70	29/–[1]	38/6	20/5	(12)	4

[1] Veno-arterial shunt of 0·5 l./min. also present.
[2] Not measured during cardiac catheterization.

All these patients were under 20 and most were under 12 years of age. They appeared to be ordinary cases of ventricular septal defect, and this was the clinical diagnosis made in all, though the combined lesion had been suspected in one. The shunts were larger than in the 15 patients with more severe stenosis discussed earlier. They averaged 8·4 litres, and were over 6·0 litres a minute in all but two, so that on the average 63 per cent of the blood from the left ventricle (instead of 40 per cent in those with gradients of from 35–99 mm.) passed to the right ventricle and back to the lungs. The pulmonary artery is, of course, slightly protected from the high pressure that might result from this but the right ventricle is not.

In four patients (Cases 62–65) the right ventricular systolic pressure was only moderately raised (under 50 mm.) and the pulmonary arterial pressure was normal. These four seem somewhere between acyanotic Fallot's tetralogy and ventricular septal defect with a normal pulmonary pressure. In the remaining four, the right ventricular pressure was rather higher (53–76 mm.) and despite the gradient the pulmonary arterial pressure also was raised (37–58 mm.); they are, therefore, more like the type of ventricular septal defect that is associated with pulmonary hypertension, and this is emphasized by the demonstration of a small veno-arterial shunt in one of them (Case 61).

The boundaries of these groups have necessarily been drawn somewhat arbitrarily. The patient

with a gradient of 35 mm. was proved to have infundibular stenosis at necropsy, and all those with gradients larger than this have been counted as having organic pulmonary stenosis. The patients with gradients below 35 mm. have been assumed to have no significant pulmonary stenosis, and were included among those with uncomplicated ventricular septal defect in the clinical part of our previous paper (Brotmacher and Campbell, 1958) but not in the section on hæmodynamic findings, because the relationship of changes in the pulmonary pressure with age would be disturbed when there was a gradient between the right ventricle and the pulmonary artery.

The Levels at which Systolic Gradients are Significant of Stenosis

Mitral stenosis and persistent ductus arteriosus are hardly ever associated with organic pulmonary stenosis, and there is no increased flow through the pulmonary valve that can play any part in producing a gradient: these groups give a picture, therefore, of the apparent gradient that may be found, e.g. from technical errors and varying conditions during the catheterization. Gradients of 12 mm. have been found in patients with *mitral stenosis* where pulmonary stenosis could reasonably be excluded.

Among 70 cases of *persistent ductus* that had been catheterized, excluding two with severe proven pulmonary stenosis, there were only four where the systolic gradient across the pulmonary valve was more than 5 mm., and in all these it was between 10 and 16 mm. Two at least of these had withdrawal tracings that seemed technically reliable. In none was there any supporting evidence of pulmonary stenosis, and when there had been a systolic murmur that might have been due to pulmonary stenosis it disappeared after the ductus had been closed. Gradients of 16 mm. or less may, therefore, be due to changing conditions and other factors and provide no reliable evidence of stenosis.

When we come to *septal defects*, a new factor has to be considered for the flow through the pulmonary valve is increased, sometimes greatly so. At the aortic valve—with a normal flow—the orifice must be reduced to about a third of the usual size before a gradient across it develops (Gorlin *et al.*, 1955). With a normal flow this is probably equally true at the pulmonary valve: a slight organic stenosis or even a relative stenosis due to a normal-sized valve ring interposed between a dilated outflow tract and a dilated pulmonary trunk may, however, produce a gradient when the flow is increased—a gradient that would be abolished if the pulmonary flow were reduced by successful closure of the defect, even if the stenosis were unrelieved. Gradients between the right ventricle and the pulmonary trunk cannot be explained as due to the large flow entirely, for they are not found with many of the larger pulmonary flows and may be found with flows that are only moderately increased. The application of these factors to our findings in eight patients with a *ventricular septal defect* and a small gradient between 15 and 31 mm. has been discussed (p. 382).

When considering similar patients with *atrial septal defect*, a level of 20 mm. was taken as the best dividing line between a systolic gradient that was significant of pulmonary stenosis and one that was not (Campbell *et al.*, 1957) for over this level there was generally some supporting evidence, such as a loud murmur, sometimes with a thrill Since then we have seen a boy aged 12 who, after many consultations, was sent to us for operation with a diagnosis of pulmonary stenosis alone: we too thought this was more important than his left-to-right shunt but, in fact, the latter was 11·6 litres a minute and at atrial level, and the pulmonary gradient was no more than 20 mm. When the atrial septal defect had been closed, the murmur that had led to the diagnosis of pulmonary stenosis disappeared. Gradients larger than this may be abolished after successful closure of the defect, showing that there is no stenosis that is significant with a normal flow.

We have now seen 16 cases of atrial septal defect with a gradient between 20 and 100 mm. It was relatively small, between 20 and 42 mm., in 10 of these 16, and probably there was little or no stenosis as the shunts were large and averaged 8·4 litres a minute. In one of these, a girl aged 14, the systolic gradient had increased from 29 to 46 mm. in five years with little change in the size of the shunt, but some at least of this was due to a Venturi effect. In the other 6, the gradient was much larger, between 70 and 90 mm.: in three of them the shunts were equally large so we are left

uncertain about organic stenosis, but in the other three it was almost certainly severe as the shunts were quite small.

Among *other patients* who have been catheterized, 12–16 mm. are the *smallest gradients* encountered where we think that other evidence supports some organic stenosis, even though it must be slight. A boy, aged 11, who was carefully observed by several physicians and was without symptoms or cardiac enlargement, was diagnosed as having a small ventricular septal defect, but at catheterization the only lesion found was infundibular stenosis with a gradient of 12 mm. A man, aged 20, with coarctation was catheterized because he had such a striking pulmonary systolic murmur and thrill, but the gradient was only 12 mm.: the signs persisted after a successful operation for coarctation. A woman, aged 41, has been under personal observation for 30 years with a diagnosis of pulmonary stenosis: catheterization revealed that she had an atrial septal defect with a left-to-right shunt of 3·5 litres a minute and a gradient across the pulmonary valve that was only 16 mm.

Summary. Our general conclusions are, therefore, that no certain significance can be attached to gradients of less than 16 mm. for they may be due to changing conditions or other technical causes. Sometimes, however, when the flow is not increased, gradients of from 12 to 20 mm. may be significant of organic stenosis, provided that the diagnosis is supported by other reliable signs and does not rest on the pressure tracings alone. A gradient larger than this is less likely to be due to outside causes; but if the pulmonary flow is increased, it must be of the order of 35 or perhaps 45 mm. before one can be reasonably sure that there is organic stenosis.

The Site of the Gradient. In atrial septal defect the gradient was always at valve level, except in one case where it was infundibular and in one where it was at both levels. With ventricular septal defects, however, the level was at the valve in 5, at the infundibulum in 11, and at both levels in 2 cases. This difference supports the view that sometimes even a small gradient has a real anatomical cause and is not due solely to the increased flow.

Discussion

Patients with pulmonary stenosis and a ventricular septal defect with a left-to-right shunt have been reported by several authors. Wood *et al.* (1954), reporting on 60 patients with ventricular septal defect, discussed shortly 11 others who had, in addition, some degree of pulmonary stenosis, 6 clinically ventricular septal defect with stenosis that was only slight and 5 clinically pulmonary stenosis that was moderate or severe. Eldridge and Hultgren (1955) reported four, and Bashour and Winchell (1955) three patients. Contro and Brostoff (1955) reported eight with gradients across the pulmonary valve of between 45 and 85 mm.: all were acyanotic at rest but two became cyanotic with easy exercise. Seven patients were studied in considerable detail by Callahan *et al.* (1955): four of them had atrial septal defects also. In a later paper, Bashour *et al.* (1957) reported eight patients between 17 and 53 years of age, with right ventricular pressures between 70 and 138 mm. and left-to-right shunts between 1·3 and 6·9 litres a minute: they were able to lead reasonably normal lives, but the oldest had become cyanotic at rest and four became cyanotic on exertion.

Relationship to Fallot's Tetralogy

This relationship is certainly a close one for patients with pulmonary stenosis and a ventricular septal defect always have two of the four features that characterize Fallot's tetralogy. If the stenosis is moderately severe they have also the third feature of right ventricular hypertrophy, which in any case is a secondary result and not a primary abnormality. We do not know whether the acyanotic patients have or have not the fourth feature—the over-riding aorta.

Significance of Aortic Over-riding. Varying degrees of this occur and the degree of over-riding may be secondary to the right-to-left shunt rather than primary. As we have pointed out (Brotmacher and Campbell, 1958), unless there is transposition, the presence or absence of a right-to-left shunt does not depend on this but on the relative pulmonary and systemic resistances. This is equally true whether the obstruction to blood flow through the lungs is offered by increased

pulmonary arteriolar resistance or by pulmonary stenosis. In our two cases with necropsies (Cases 71 and 78) there was nothing in the relationship between the aortic root and the ventricular septal defect to distinguish them from cases of classical Fallot's tetralogy, although Case 78 was still acyanotic when he died at the age of 19.

That over-riding of the aorta may be present without cyanosis is proved by the condition of many patients with Fallot's tetralogy who have had an unusually successful operation, generally a valvotomy or infundibular resection, and have become good examples of *acyanotic Fallot's tetralogy*. Campbell *et al.* (1954) discussed some of these who had been recatheterized after operation and five of those recorded in their Table VI were acyanotic, with an arterial oxygen saturation between 92 and 98 per cent, although it had averaged as low as 81 per cent before operation. The pulmonary flow was now larger than the systemic flow, the average proportion being 3 to 2, although before operation it had been 1 to 2; the right ventricular pressure was hardly changed and the degree of over-riding of the aorta was, of course, the same. Only in one girl had the pulmonary pressure risen above normal (from 14/7 to 38/12). She has remained very well clinically for seven years and is an excellent example of acyanotic Fallot's tetraology. Wood also (1956) has seen several cases of this type.

Development of Cyanosis. The patients who had had successful operations are certain examples of acyanotic Fallot's tetralogy. Are there others who may justly be described as such? Generally in Fallot's tetralogy cyanosis becomes noticeable in infancy, in our experience before eighteen months, though exceptionally it may be much later. One deeply-cyanosed man, aged 29 when he died, had so little disability or cyanosis until three years before his death, that he was thought to have pulmonary stenosis with a closed ventricular septum rather than Fallot's tetralogy, which was, however, demonstrated at necropsy. We have seen a few other patients where cyanosis has not been noted for several years after birth. Brown (1950, p. 196) says it is exceptional but mentions one such man where the diagnosis was established at necropsy when he died at the age of 29. Wood (1956), however, says that 15 per cent of his patients with Fallot's tetralogy had not developed cyanosis at rest when they were seen. Wood *et al.* (1954) discussed 10 cases described as acyanotic Fallot's tetralogy but the distinction between these and others described as cases of ventricular septal defect and pulmonary stenosis is not clear.

Admittedly some patients with Fallot's tetralogy have much less cyanosis than others and sometimes it may be slight except on exertion. It is, therefore, possible but unlikely that one may see some cases of classical Fallot's tetralogy in an apparently pre-cyanotic stage. When our 15 cases with pulmonary stenosis and a ventricular septal defect were first seem, two only had also a small right-to-left shunt at rest and three probably became slightly cyanotic on exertion, but all were clinically acyanotic and the shunt was entirely or mainly left-to-right. During the time they were under observation (up to seven years) two became slightly cyanotic at rest and two more became cyanotic on exertion, so that they were more difficult to distinguish from classical Fallot's tetralogy. A longer follow-up is therefore needed to know if the others will do this, but we think that most of them would have done so earlier and more completely if they were going to do so at all, for they still had a moderate left-to-right shunt which would have to be abolished or greatly reduced. A large left-to-right shunt is not found with classical Fallot's tetralogy: a small one can sometimes be demonstrated (Holling, 1952) but in our experience, when it is present, it is generally less than one litre a minute.

Whether the condition from which our patients are suffering is termed ventricular septal defect with pulmonary stenosis or acyanotic Fallot's tetralogy is, therefore, mainly a matter of nomenclature. One cannot say that the latter term is inaccurate, but there is not much object in it unless central cyanosis is going to develop later, because this is such a cardinal feature of Fallot's tetralogy. As we have shown, cyanosis at rest develops only in a minority and it is not possible to predict which patients will develop this: further, many are still without cyanosis on exertion. Partly because of this and partly because most of our patients still have a moderate left-to-right shunt we think it better to describe the condition as ventricular septal defect with pulmonary stenosis.

Surgical Treatment

The left-to-right shunts in our 15 acyanotic patients were only moderate, averaging 3·2 litres and being 5·2 litres a minute or less in all but one. This shows that in these patients pulmonary stenosis has advantages as well as drawbacks. We think that pulmonary valvotomy or infundibular resection is contra-indicated unless the ventricular septal defect can be closed at the same time, even when the stenosis is severe enough to produce a right ventricular systolic pressure approaching the systemic. The patient would presumably have a large instead of a moderate-sized shunt, and would then be likely to develop an increased pulmonary arteriolar resistance that would probably rise over the years and again expose him to the risk of developing a right-to-left shunt, for which nothing could be done.

These considerations apply even more strongly to patients who are acyanotic with exercise and to those in whom the gradient is small, for sometimes the pulmonary arterial pressure is raised in spite of the stenosis. Contro and Brostoff (1955) agree that valvotomy alone should not be carried out in patients with pulmonary stenosis and a left-to-right shunt through a ventricular septal defect. Bashour *et al.* (1957) think that the prognosis is too good to justify the risks of surgical treatment. Possibly, however, operation may be the best course at present available if the right ventricular pressure becomes high enough to produce a right-to-left shunt of considerable size even at rest.

We have referred to some of our patients with Fallot's tetralogy where the cyanosis was trivial except on exertion. At first, when considering surgical treatment for them, we were hesitant about advising it, for there is some correlation between the degrees of cyanosis and of disability though not a very close one. We remember particularly two patients who were very disabled but hardly cyanotic until they exerted themselves: when an anastomotic operation had been carried out they did in fact benefit as much as most others and have maintained their improvement, although the right-to-left shunt must have been small at rest. We have, however, no reason to think that these patients had appreciable left-to-right shunts before operation, and they became very cyanotic on exertion.

When there is a significant left-to-right shunt, pulmonary valvotomy is contra-indicated until the ventricular septal defect can be closed with relative safety.

Summary and Conclusions

We are reporting 15 patients who had a ventricular septal defect with a left-to-right shunt and pulmonary stenosis in addition. Initially all these were clinically acyanotic and all had a left-to-right shunt, although two had also a small right-to-left shunt and three probably became cyanotic on exertion. During subsequent years two have become slightly cyanotic, even at rest.

The diagnosis in most of them was ventricular septal defect because of the hæmodynamic effects of the left-to-right shunt, but sometimes pulmonary stenosis and rarely both lesions were suspected. In retrospect, the degree of right venticular preponderance electrocardiographically, in the absence of clinical pulmonary hypertension, should have led to the combined diagnosis more often.

Generally, the disability of these patients was not great, though often they had a large heart. A history of squatting was unusual.

Patients with Fallot's tetralogy rarely have a left-to-right shunt that exceeds one litre a minute and generally have a right-to-left shunt large enough to make them obviously cyanotic even at rest. Nevertheless, the dividing line between this condition and Fallot's tetralogy is rather narrow. Our patients were chosen on the diagnosis made after catheterization rather than on any rigid definition laid down beforehand, but now that we have studied them we think the main feature that justifies separating them is the combination of a left-to-right shunt that is relatively large and a right-to-left shunt that is trivial or absent at rest though sometimes developing on exertion. The right-to-left shunt may gradually become larger so that the condition becomes difficult to distinguish from classical Fallot's tetralogy, but this seems to be unusual.

We think it is better to speak of "ventricular septal defect with pulmonary stenosis" than of

"acyanotic Fallot's tetralogy." The evidence suggests that over-riding of the aorta is not important in determining the type of shunt. The present cases have, therefore, the same relationship to Fallot's tetralogy that ventricular septal defect has to Eisenmenger's complex, but the change to the cyanotic state is much less certain. The ordinary case of Fallot's tetralogy is one where the stenosis had been severe enough to produce a right-to-left shunt from birth or from an early age.

We have also discussed more shortly eight patients with systolic gradients of less than 35 mm., in most of whom we think there is no organic obstruction. Such gradients cannot by themselves be taken as reliable evidence of stenosis, though in general, if the pulmonary flow is normal, even gradients of about 20 mm. may indicate a real, if slight, organic stenosis. Larger gradients than 40 mm. generally indicate a real organic narrowing, even when the flow is increased, though it may not be enough to produce significant obstruction if the flow can be reduced to normal.

Until ventricular septal defects can be closed with reasonable safety, we do not advise any surgical treatment for patients in this group, as the pulmonary stenosis, though throwing extra work on the right ventricle, reduces the size of the left-to-right shunt and so may prevent the patient developing pulmonary hypertension.

References

Baylis, J. H., Campbell, M., Gilmore, H. R., and Hudson, R. (1955). *Guys Hosp. Rep.*, **104**, 114.
Bashour, F., and Winchell, P. (1955). *Ann. intern. Med.*, **42**, 1227.
——, Redington, J., and Winchell, P. (1957). *Dis. Chest.*, **31**, 423.
Brotmacher, L., and Campbell, M. (1958). *Brit. Heart J.*, **20**, 97.
Brown, J. W. (1950). *Congenital Heart Disease*. 2nd ed., Staples Press, London.
Callahan, J. A., Brandenburg, R. O., and Swan, H. J. C. (1955). *Circulation*, **12**, 994.
Campbell, M. (1954). *Brit. Heart J.*, **16**, 273.
——. Deuchar, D., and Brock, R. C. (1954). *Brit. med. J.*, **2**, 111.
——, Neill, C., and Suzman, S. (1957). *Brit. med. J.*, **1**, 1375.
Contro, S., and Brostoff, P. (1955). *Amer. Heart J.*, **50**, 543.
Eldridge, F. L., and Hultgren, H. N. (1955). *Amer. Heart J.*, **49**, 838.
Gorlin, R., McMillan, I. K. R., Medd, W. E., Matthews, M. B., and Daley, R. (1955). *Amer. J. Med.*, **18**, 855.
Holling, H. E. (1952). *Clin. Sci.*, **11**, 283.
Mannheimer, E., Ikkos, D., and Jonsson, B. (1957). *Brit. Heart J.*, **19**, 333.
Wood, P., Magidson, O., and Wilson, P. A. O. (1954). *Brit. Heart J.*, **16**, 387.
—— (1956). *Diseases of the Heart and Circulation*. 2nd ed. Eyre and Spottiswode, London.

THE ROLE OF VENOUS CONSTRICTION IN CIRCULATORY DISORDERS

BY

JÁNOS P. RADÓ, ENDRE GONDA, AND ERWIN KOVÁCS

From the Department of Medicine No. 2, the János Hospital, Budapest

Received October 22, 1957

The role of active venous function in the regulation of normal and pathological circulation has been dealt with in an increasing number of reports. As a matter of fact, this conception is not new, its outlines having been laid down decades ago (Goltz, 1864; Bayliss and Starling, 1895; Hooker, 1920; Donegan, 1922; Fleisch, 1930, and others). In a monograph written 25 years ago Gollwitzer-Meyer summed up all the aspects of the problem known up to those days, and emphasized that the asphyxia, hypoxia, and hypercapnia increase not only the arterial but, as a consequence of the constriction of the veins, also the venous pressure. These data have of late been confirmed both in man and animal by the use of more refined techniques (Alexander, 1954; Duggan *et al.*, 1953; and Page *et al.*, 1955). Roy and Sherrington proved as early as 1890 that as a consequence of nervous stimulation venous pressure increased, that is, the veins constricted. Fleisch (1930), assumed the existence of a venomotor centre regulating venous function. Several investigations (Doupe *et al.*, 1938; Duggan *et al.*, 1953; Page *et al.*, 1955; and Alexander, 1954 and 1955) left no doubt that active venous function depended on venomotor regulation (venomotor tone) the increase of the latter causing the constriction of the veins. According to Gollwitzer-Meyer (1932), Green *et al.* (1943), and Guyton (1951), the activity of the vasomotor centre causes oscillations in the arterial tone (as after Alexander's experiments, 1955) that run parallel with the variations of the venomotor tone. Thus, under normal conditions there is a mechanism that provides for parallel changes in the arterial and venous tone. Venoconstriction in congestive heart failure was suggested first by Starling (1909) and its significance has been strongly emphasized by McMichael (1946, 1949). Sharpey-Schafer (1944) found that patients with grave anæmia in heart failure developed an increase of venous pressure in spite of the fact that the circulating blood volume and the arterial blood pressure were low; only a venous constriction could be held responsible for this. This mechanism obviously plays an important part also in other forms of heart failure, in addition to the significance of the increase of the effective circulating blood volume (Warren and Stead, 1944; Starr and Rawson, 1946; Starr, 1949; Mc Michael, 1949). While in congestive heart failure the constriction of the veins brings about sensitiveness to the variations of the circulating blood volume (Warren and Stead, 1944; Richards *et al.*, 1937; McMichael, 1948) the venous pressure in animals with a normal circulation can be raised only by an extreme increase of the circulating plasma volume (Huckabee *et al.*, 1950; Landis *et al.*, 1946). It has been shown that antihypertensive drugs, such as aminophyllin, TEAB, TEAC, priscol, dibenamin, sodium nitrite, and hexamethonium, decrease the venous pressure in congestive heart failure (Howarth *et al.*, 1947; Steinberg and Hensen 1946; Matthes *et al.*, 1951; Heinrich and Weissbecker, 1955; Hayward, 1948; Duchon *et al.*, 1953; Relman and Epstein, 1949; Braun and Fryd, 1951; Fejfar and Brod, 1951; Halmágyi *et al.*, 1952; Kelley *et al.*, 1953; and Burch, 1954). It is to be supposed that in congestive heart failure these drugs, besides other effects, decrease the venous pressure by eliminating the venous constriction (increased tone).

In this report we wish to deal with the effects of an antihypertensive agent, sodium nitrite, on the venomotor tone of patients with circulatory disorders, heart failure, and hypertension, as well as on that of normal controls.* Attempts have been made to analyse the role of the venous constriction in the various phases of congestive heart failure on the one hand, and to use the measurements of the fall in venous pressure induced by sodium-nitrite, alongside the measurements of venous pressure, as a means of judging the effectiveness of treatment in heart failure, on the other hand.

The 121 test subjects were placed in four groups.

(1) 27 controls, with a normal circulation.

(2) 28 patients with congestive heart failure, including 8 with hypertension and 20 with a normal blood pressure, i.e. not exceeding 150/90 mm. Hg. Cardiac failure resulted from rheumatic disease, cardiosclerosis, cardiovascular syphilis, or from other causes.

(3) 25 patients, in whom preceeding failure had been fully relieved by adequate treatment.

(4) 41 patients with hypertension, but without symptoms and signs of congestive heart failure. Most of these were old and arteriosclerotic, but 8, aged 20 to 35 years, with a normal circulation were used as controls to exclude the effects of age, arteriosclerosis, and latent failure.

Venous pressure was measured from the antecubital vein by means of the Móritz-Tabora instruments, from which the level of the water column above the angle of Ludivic was read in mm.: to this value we added 4 cm. Sodium nitrite in a dose of 0·06 g. was injected into the antecubital vein of the contralateral arm and the changes in the water column were recorded.

Results

In the 27 subjects with a normal circulation, venous pressure ranged from 48 to 133 and averaged 79 mm. water (Fig. 2): it was above 100 mm. in one-third of the cases. The fall induced by sodium nitrite averaged 7 mm. water, exceeding 15 mm. in a single case. The reduction, as determined by the test for the mean of a unique sample, is significant ($P<0·001$). On the basis of these data a fall exceeding 15 mm. water has been accepted as being pathological.

The mean venous pressure in the 28 patients with congestive heart failure was 187 mm. water (Fig. 2). The fall induced by sodium nitrite averaged 58 mm. (31%). It can be seen in Fig. 1 that (*a*) sodium nitrite causes a greater fall when venous pressure is high, but (*b*) the fall is relatively greater when venous pressure is low. Sodium nitrite effected a 50 per cent reduction of venous pressures below 100 mm., and a 25 per cent reduction of those above 200 mm. water.

The response to sodium nitrite of the 8 patients with hypertension and congestive heart failure is comparable with that given by patients with failure and a normal pressure. The average venous pressure of 170 mm. water was reduced by 32 per cent (55 mm.). In the 25 patients, who had been decompensated but were compensated clinically at the time of the test, venous pressure averaged 55 mm.; this was reduced on sodium nitrite by 40 per cent (22 mm.).

In these measurements it was found useful to examine the venous reaction to sodium nitrite, as by this method the process of compensation could be followed up (Fig. 3). This method supplemented the measurement of venous pressure, which is one of the objective means for judging compensation. It has been found particularly useful in the phase when the patient is still decompensated, though the venous pressure is already "normal." Comparative analysis will reveal that the difference in the fall of venous pressure between the decompensated and already compensated patients is significant ($P<0·001$). Applying the t test for the mean of a unique sample to identical groups of the two categories ($P<0·001$) and for comparison of two means with a non-identical group ($P<0·001$) the values obtained are both highly significant.

We have taken the opportunity to study also the venous depressor action of kombetin, digitalis, and novurit (a mercurial diuretic) in comparative tests. It is clear from Fig. 4 that the decrease in

* For simplicity's sake we do not deal in our present study with the role of the following factors influencing the venous pressure: redistribution of blood, tissue tension-respiratory variations, and limb muscle movements.

venous pressure induced by novurit in 24 hours is almost equal to that effected by digitalis glycosides in several days. The patients were subjected to the so-called slow digitalization. It can be seen that in most cases, novurit lessened but slightly the fall of the venous pressure induced by sodium nitrite, but the venous pressure itself had fallen considerably.

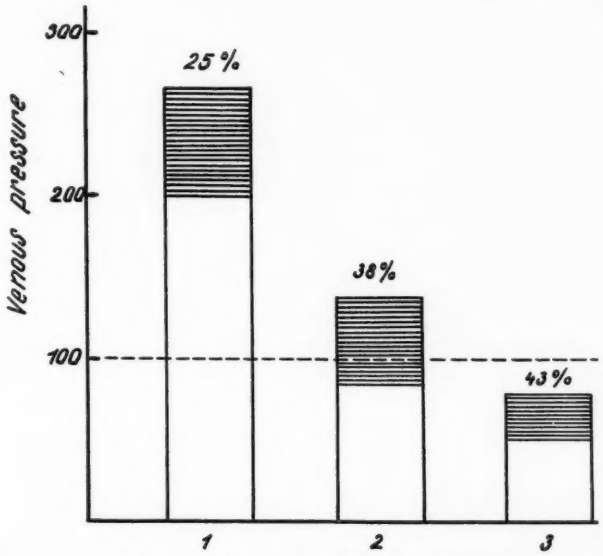


FIG. 1.—The ratio of the fall in pressure induced by sodium nitrite, indicated by the shaded area, to the venous pressure in the range (1) of 200 to 300 mm. of water, (2) of 100 to 200 mm. of water, and (3) below 100 mm. of water.

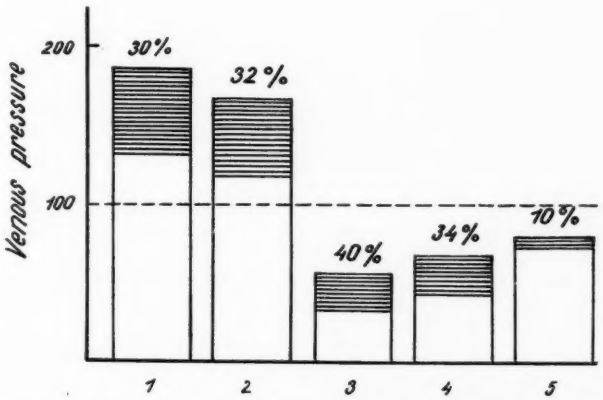


FIG. 2.—The venous pressure and the reduction in pressure induced by sodium nitrite, indicated by the shaded area, in cases of (1) congestive heart failure with normal blood pressure, (2) congestive heart failure with hypertension, (3) congestive heart failure after compensation, (4) hypertension without heart failure, and (5) normal control subjects.

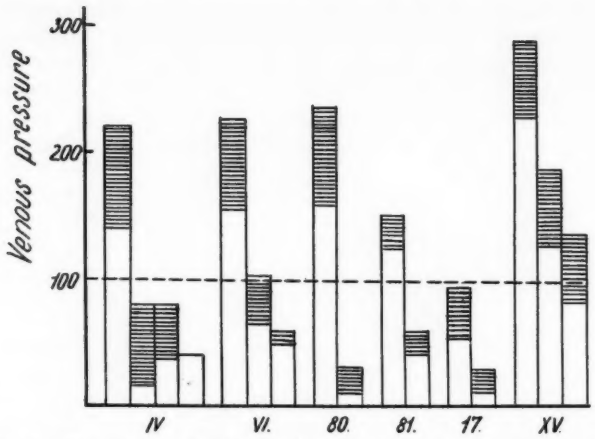


FIG. 3.—The groups of columns show the measurements made in one patient. In Case XV cardiac treatment had not been completed. The shaded area indicates the fall of pressure induced by sodium nitrite.

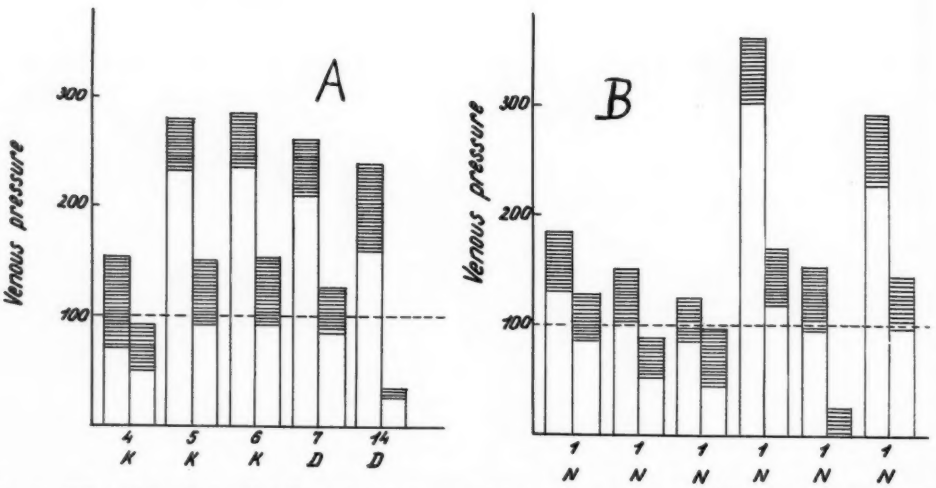


FIG. 4.—Effect of kombetin, digitalis, and novurit, on venous pressure and on the fall induced by sodium nitrite. The shaded area indicates the fall in venous pressure, induced by sodium nitrite.

In (A) K=kombetin, D=digitalis; in (B) N=novurit. The double columns show the measurements made in one patient. The patients were still in congestive heart failure at the time of both measurements, but the second measurement of the last case in (A) was made in compensation. The numerical values designate the number of days that elapsed between two measurements.

The control measurements made in patients with hypertension revealed that, although they were not decompensated, they responded to sodium nitrite with a fall in venous pressure, which was greater than that shown by subjects with a normal pressure and circulation. In the 41 compensated patients with hypertension, venous pressures averaged 68 mm. of water, which was reduced by 34 per cent (23 mm.) on sodium nitrite. The 8 controls showed an average venous pressure of 85 mm., falling by 27 per cent (23 mm.) on sodium nitrite.

This means that patients with a raised blood pressure respond to sodium nitrite with a greater fall of venous pressure than the patients where it is normal. As determined by the t test for the mean of unique sample the decrease of venous pressure is significant ($P<0.001$). The data for the statistical analysis for the different groups are comprised in Tables I, II, and III.

We have made 180 measurements in 120 patients. In 5 of these, an episode of circulatory collapse occurred. The arterial blood pressure decreased in every case, *without a fall in venous pressure*. In one, the circulation time increased from 16 to 40 seconds.

TABLE I

THE FALL IN VENOUS PRESSURE INDUCED BY SODIUM NITRITE IN CONTROL SUBJECTS AND IN HYPERTENSIVE PATIENTS

	Number of cases	Mean fall in venous pressure (water mm.)	Standard deviation (water mm.)	t	P	Significance
Control subjects	27	7	7·5	4·8	⩽0·001	very high
Hypertensive patients without heart failure, over 35 years	33	21·3	12·0	10·2	⩽0·001	very high
Hypertensive patients without heart failure aged 20 to 35 years	8	27·5	13·2	5·9	⩽0·001	very high

TABLE II

THE FALL IN VENOUS PRESSURE INDUCED BY SODIUM NITRITE IN PATIENTS WITH PREVIOUS HEART FAILURE (GROUP I) AND IN THOSE COMPENSATED BY TREATMENT (GROUP II)

	Number of cases	The difference in the mean fall of venous pressure in the two groups (water mm.)	Standard deviation (water mm.)	t	P	Significance
Same patients in the two groups, before and after compensation	8	45·1	23·0	5·5	⩽0·001	very high
Different patients in the two groups, before and after compensation	53	32·1	13·6	7·2	⩽0·001	very high

TABLE III

COMPARISON OF THE VENOUS DEPRESSOR EFFECT OF SODIUM NITRITE IN CONTROL SUBJECTS AND IN PATIENTS

	Venous pressure	water (mm.)	water (mm.)	water (mm.)	water (mm.)	water (mm.)
		40–59	60–79	80–99	100–119	120–139
Average fall in venous pressure induced by sodium nitrite	in normal controls (Group I)	7·5	13·2	6·8	6·5	5·8
	in hypertensive patients without heart failure and patients with earlier heart failure compensated by treatment (Group II)	22·7	22·9	26·0	29·0	15·0
	in patients with heart failure (Group III)	—	37·5	42·9	42·7	47·5

Discussion

The venomotor changes, which take place parallel with the arterial reactions under physiological conditions, show dissociation in pathological conditions. For instance, in our normal subjects sodium nitrite induced practically no lowering of venous pressure and only a very slight depression of arterial pressure. In compensated hypertension both the arterial and venous pressure were lowered. In the decompensated patients with normal blood pressure, arterial pressure was slightly, and venous enormously reduced. In the decompensated patients with hypertension the situation was similar to this, except that here the arterial pressure dropped more. These data reveal that under pathological conditions we do not find the correlation that exists under physiological conditions between the arterial and the venous tones. In such cases venous pressure has its own, relatively independent, regulation.

It is noteworthy that in congestive heart failure associated with high venous pressure, the fall brought about by sodium nitrite was greater than in cases with lower venous pressure; if, however, expressed as a percentage of the total venous pressure, it was relatively smaller. This indicates that alongside the increased venomotor tone, the decisive role in extreme venous pressure is played by hypervolæmia (the rise of the effective circulating blood volume). As soon as the vicious circle of decompensation is broken, hypervolæmia diminishes faster than the increased venomotor tone and the significance of the latter in venous pressure gains preponderance. These considerations are supported also by the measurements made after the administration of novurit, in which in the majority of our cases, the venomotor tone decreased but slightly, whereas venous pressure diminished more, indicating that ample diuresis reduced hypervolæmia.

In conclusion, it can be stated that, at the onset of treatment for decompensation, hypervolæmia is first of all to blame for the high venous pressure, although the absolute value of the venomotor tone is very high. In the course of treatment the latter decreases, but relatively it increases. The increase of venomotor tone has been found to be so characteristic of heart failure that its examination for diagnostic purposes is recommended. There are certain objective methods, by which the effectiveness of cardiac treatment can be appraised (for example repeated comparative studies of the circulation time). Repeated comparative tests for the lowering of venous pressure on sodium nitrite are recommended for such purposes.

Further, the compensated cardiac patient responds to sodium nitrite with an abnormally large fall in venous pressure. The data obtained by the method we have employed differ from the results published by Relman and Epstein (1949), Burch (1954 and 1955), and Wood and Litter (1956) according to which the venomotor tone is increased during decompensation but returns to normal in compensation. It seems, if we reverse the sequence of observations, that at the onset of cardiac decompensation the rise of venous pressure begins with an increase of venomotor tone, and that the hypervolæmia gains increased significance only later.

We observed strikingly low venous pressures in patients who reached the optimal compensation and it was further decreased by sodium nitrite: the reason is not yet clear. In our opinion, the phenomena we observed may perhaps throw light on Sjöstrand's findings (1950) that in some patients the circulating blood volume after optimal compensation is lower than the normal.

Many patients with œdema have been found to have venous pressures lower than 40 mm. water. On the other hand, venous pressures as high as 130 mm. occurred in normal subjects with no circulatory disorder. The former responded well to sodium nitrite, while the latter showed hardly any response. For this reason we cannot say that a venous pressure within the normal limits (up to 100 mm. water or higher) is normal or pathological, but in case the sodium nitrite test reveals the presence of an increased venomotor tone by the resulting fall exceeding 15 mm., there is good reason to claim that venous pressure is pathological. Venous pressure and the fall resulting in it have been compared in the following three groups of patients: (1) patients with a normal circulation, (2) patients with hypertension without decompensation, though some had a history of decompensation, and (3) patients with decompensation. The difference between the three groups is significant, P being $<0{\cdot}001$ by the permutation method. The fall is the smallest in Group I,

and highest in Group 3 ($P<0{\cdot}001$). These data have been summed up in Table III. The data support the view that in the venous pressure range of 40 to 139 mm. water, among subjects showing comparable pressures, venous tone is the lowest in the normal subjects, highest in the decompensated patients, with the values for slight latent decompensation occupying an intermediate position between the two (Dr. Ireneus Juvancz).

We have found the venomotor tone slightly increased in our hypertensive patients, in whom venous pressure was, in general, normal. The same has been observed in young subjects with hypertension and a normal circulation. It appears that in hypertension the arteriolar constriction is associated with a slight venoconstriction.

The five cases in which venous pressure did not change in collapse merit particular attention. Two similar cases have been reported by Halmágyi *et al.* (1952). The mechanism of this is not yet clear. It is worth while comparing congestive heart failure with shock, from the point of view of venomotor tone. In shock this mechanism ensures for a time the maintenance of the minute volume and circulation (Meek, 1921; Holt *et al.*, 1946; Hickam and Pryor, 1951; Alexander, 1955; and Page *et al.*, 1955). In decompensation the increased venomotor tone serves to enhance venous filling, which in turn increases cardiac output according to Starling's law.

The mechanism will be reversed when the further rise of venous pressure renders the heart incapable of taking up the total volume of blood flowing to it and the Starling curve declines. In such cases a further increase of venomotor tone overstrains the heart and accelerates the development of the vicious circle of decompensation. On the other hand, a decrease of venomotor tone improves the work of the heart. So hexamethonium and veratrin decrease the cardiac output (Currens *et al.*, 1953; Crumpton *et al.*, 1954) in hypertensive patients without heart failure, but increase it in those with congestive heart failure—just as sodium nitrite and TEAB do (Kelley *et al.*, 1953; Burch, 1955; Relman *et al.*, 1949; and Halmágyi *et al.*, 1952). In hypertensive patients with heart failure the antihypertensive drugs increase the cardiac output by decreasing venous pressure, that is the unduly raised venomotor tone, and they play a part in raising the heart onto the ascending limb of the Starling curve. Such a mechanism accounts for their beneficial clinical effect in restoring compensation (Hayward, 1948; Lyons *et al.*, 1947; Burch, 1955; and Kelley *et al.*, 1952). In diseases of the circulation, especially in congestive heart failure and shock, the examination of the venomotor tone will not only permit a deeper insight into pathogenesis, but will influence the therapeutic measures as well.

Summary and Conclusions

The effect of sodium nitrite on venous pressure was examined in congestive heart failure, in hypertensive disease without heart failure, and in control subjects with a normal circulation. The investigations were repeated in the course of the treatment of heart failure and also when reaching the optimal compensation.

It has been found that (1) in every phase of heart failure, (2) in patients reaching the optimal compensation, and (3) in hypertensive disease without heart failure, the venous pressure has fallen under the influence of sodium nitrite more than in control subjects.

In the three following groups, (1) control subjects, (2) hypertensive patients without heart failure or those with previous heart failure that has become compensated by treatment, and (3) patients with heart failure, the fall of venous pressure of the cases with equal venous pressure was lowest in the first group, highest in the third group, and intermediate in the second group.

The fall of venous pressure induced by sodium nitrite did not correlate with the decrease of arterial pressure. In our opinion the fall of venous pressure induced by sodium nitrite results from a suppression of venoconstriction, by decreasing the increased venomotor tone. Our investigations suggest that the increase of venomotor tone in cardiac decompensation is an early and common phenomenon.

The effect of sodium nitrite can be used also as a test to decide whether the increased venoconstriction plays a role in the venous pressure beyond or within the normal range. With its help the improvement of heart failure can be followed.

The first part of our investigations was made in the Rókus Hospital, 1953–1954, the second part in the János Hospital, 1955, Budapest.

We are most deeply indebted to the late Professors Imre Schill and Imre Fodor for their advice and assistance. The statistical computations by Dr. Ireneus Juvancz are also gratefully acknowledged.

References

Alexander, R. S. (1953). *Circulat. Res.*, **1**, 271.
—— (1954). *Circulat. Res.*, **2**, 405.
—— (1955). *Circulat. Res.*, **3**, 181.
Bayliss and Starling (1895). Quoted by Gollwitzer-Meyer (1932).
Bolton, C. (1917). *Brit. med. J.*, **1**, 642.
Braun, J., and Fryd, C. H. (1951). *Brit. Heart J.*, **13**, 294.
Brod, J., Fejfar, Z., Fejarova, M. H., and Kotanove, E. (1951). *Sborn, Lék. Praha.*, **53**, 128 and 154.
Burch, G. E. (1954). *Arch. intern. Med.*, **94**, 724.
—— and Ray, C. T. (1951). *Amer. Heart J.*, **41**, 918.
—— (1955). *Circulation*, **11**, 271.
Crumpton, C. W., Rowe, G. G., O'Brien, G., and Murphy, Q. R., Jr. (1954). *Circulat. Res.*, **2**, 79.
Currens, J. H., Myers, G. S., and White, P. D. (1953). *Amer. Heart J.*, **46**, 576.
Donegan (1922), quoted by Gollwitzer-Meyer, K. (1932).
Doupe, J., Krynauw, R. A., and Snodgrass, S. R. (1938). *J. Physiol.*, **92**, 383.
Douchon, J., Havier, V., and Hifka, D. (1953). *Brat. Lek. Listy*, **33**, 555. Quoted by Halmágyi, D. (1954). *Orvosi Hetilap*, **95**, 1109.
Duggan, J. J., Love, L., and Lyons, R. H. (1953). *Circulation*, **7**, 869.
Eisenberg, S. (1954). *Circulation*, **10**, 902.
Fejfar, Z., and Brod, J. (1951). *Sborn. Lék. Praha*, **53**, 99.
Fleisch, A. (1930 and 1931). *Pflüg. Arch. ges. Physiol.*, **225**, 26 and 226, 393.
Gollwitzer-Meyer, K. (1932). *Ergebn. Physiol.*, **34**, 1145.
Goltz (1864). *Arch. Path. Anat. Physiol.*, **29**, 394.
Green, H. D., Lewis, R. N., and Nickerson, N. D. (1943). *Proc. Soc. exper. Biol. Med.*, **53**, 228.
Guyton, A. C., and Harris, J. W. (1951). *Amer. J. Physiol.*, **165**, 158.
Halmágyi, D., Felkai, B., Iványi, J., and Hetényi, G., Jr. (1952). *Brit. Heart J.*, **14**, 101.
Hayward, G. W. (1948). *Lancet*, **1**, 18.
Heinrich, K., and Weissbecker, L. (1955). *Münch. med. Wschr.*, **9**, 260.
Hickam, J. B., and Pryor, W. W. (1951). *J. clin. Invest.*, **30**, 401.
Hooker (1920). *Amer. J. Physiol.*, **54**, 30.
Holt, J. P., Rashkind, W. J., Bernstein, R., and Greisen, J. C. (1946). *Amer. J. Physiol.*, **146**, 410.
Howarth, S., McMichael, J., and Sharpey, Schafer, E. (1947). *Clin. Sci.*, **6**, 41 and 125.
Huckabee, W., Casten, G. G., and Harrison, T. R. (1950). *Circulation*, **4**, 343.
Kelley, R. T., Freis, E. D., and Higgins, T. F. (1953). *Circulation*, **7**, 169.
Landis, E. M., Brown, E., Foureaux, N., and Wise, C. (1946). *J. clin. Invest.*, **25**, 234.
Litter, R. W. (1954). *J. clin. Invest.*, **33**, 953.
Lyons, R. H., Moe, G. K, Neligh, R. B., Hoobler, S. W., Campbell, K. N., and Rennick, B. R. (1947). *Amer. J. med. Sci.*, **213**, 315.
Matthes, K. (1951). *Kreislaufuntersuchungen am Menschen mit fortlaufend registrierenden Methoden. Georg Thieme Verlag*, Stuttgart. 93 p.
McMichael, J. (1946). *Schweiz. med., Wschr.*, **76**, 851.
—— (1948). *Brit. med. J.*, **2**, 927.
—— (1949). *Amer. J. Med.*, **6**, 651.
Meek (1921). *Amer. J. Physiol.*, **16**, 1.
Merril, A. J., Morrison, J. L., and Brannon, E. S. (1946). *Amer. J. Med.*, **1**, 468.
Page, E B., Hickam, J. B., Sieker, H. O., McIntosh, H. D., and Pryor, W. W. (1955). *Circulation*, **11**, 262.
Relman, A. S., and Epstein, F. H. (1949). *Proc. Soc. exper. Biol. Med.*, **70**, 11.
Richards, D. W., Caughey, J. L., Cournand, A., and Chamberlain, F. L. (1937). *Trans. Ass. Amer. Physns.*, **52**, 250
Starr, I., Jeffers, W. A., and Meade, R. H., Jr. (1943). *Amer. Heart J.*, **26**, 291.
—— (1949). *Ann. intern. Med.*, **30**, 1.
—— and Rawson, A. J. (1946). *Amer. med. Soc.*, **199**, 27.
Sharpey-Schafer, E. (1944). *Clin. Sci.*, **5**, 125.
Sjöstrand, T. (1950). *Nord. Med.*, **43**, 155.
Steinberg, F. M. U., and Hensen, J. (1946). *J. Lab. clin. Med.*, **31**, 857.
Warren, J. W., and Stead, E. A., Jr. (1944). *Arch. intern. Med.*, **73**, 138.
Weiss, S., Willkins, R. W., and Haynes, Fw. (1937). *J. clin. Invest.*, **16**, 73.
Willkins, R. W., Haynes, F. W., and Weiss, S. (1937). *J. clin. Invest.*, **16**, 85.
Wood, J. E., and Litter, R. W. (1956). *Circulation*, **13**, 524.

PULMONARY FUNCTION IN PULMONARY HYPERTENSION

BY

M. B. McILROY AND G. H. APTHORP

From the Institute of Cardiology and the Medical Unit, St. Bartholomew's Hospital

Received November 1, 1957

It has been shown by cardiac catheterization that an increased resistance to blood flow through the lungs occurs in four main conditions: (1) congenital heart disease with potential shunt, (2) mitral valve disease or left ventricular failure, (3) chronic lung disease, and (4) primary and thromboembolic pulmonary hypertension. Although the burden of an increased pulmonary vascular resistance falls almost entirely on the circulation, the primary lesion is probably in the lungs. Up to now little has been written about the effect of pulmonary hypertension on pulmonary function and the object of this paper is to report a study of the mechanical properties of the lungs and the diffusing capacity in a group of patients in whom the presence of a raised pulmonary vascular resistance was established by cardiac catheterization.

Material and Methods

Of the 27 patients investigated, 17 had congenital heart disease with a shunt at atrial, ventricular, or ductal level which was usually bi-directional. In no case was the pulmonary blood flow increased, and in all there was clinical and laboratory evidence of an increased pulmonary vascular resistance. In 5 patients mitral valve disease was complicated by pulmonary hypertension with a pulmonary vascular resistance of 10 units (800 dyne sec./cm.$^{-5}$) or more. In one case pulmonary hypertension was associated with chronic pulmonary fibrosis, while in the remaining four a diagnosis of primary pulmonary hypertension was made on clinical grounds and confirmed by cardiac catheterization. The relevant physiological findings are given in Table I. In 25 cases pulmonary arterial pressure and pulmonary blood flow were measured; in the other two only right ventricular pressure tracings were obtained, but the clinical findings left no doubt that the pulmonary vascular resistance was raised.

Pulmonary function studies were carried out at rest with the patient sitting in a chair and either during exercise on a motor-driven treadmill or after the patient had walked upstairs. The aspects of pulmonary function studied included the compliance of the lungs, the respiratory resistance, the diffusing capacity of the lungs for carbon monoxide (Dco), the helium mixing curve, and the ventilation equivalent for oxygen (O_2/V) during exercise. Compliance in l./cm. H_2O is a measure of the pressure required to overcome the elastic recoil of the lungs, and respiratory resistance in cm. H_2O/l./sec. expresses the resistance to air flow in the bronchial tree. The measurement of Dco in ml.O_2/min./mm. pO_2 is an overall measure of the rate of transfer of oxygen into the pulmonary capillary blood: it is influenced by any disturbance of the normal balance between alveolar ventilation and perfusion as well as by abnormality of the alveolar membrane. The helium mixing curve measures the equality of the distribution of ventilation to different parts of the lungs and if it is normal, any reduction in Dco must be due to inequality of perfusion or abnormality of the alveolar membrane. The ventilation equivalent for oxygen in ml. O_2/l. ventilation expresses the oxygen uptake for a given ventilation and, since oxygen uptake is related to the grade of exercise, the ventilation equivalent measures the efficiency of ventilation.

The compliance and respiratory resistance of the lungs were measured from simultaneous tracings of intra-œsophageal pressure and tidal volume. The pressure in the œsophagus was measured by the method described by Mead *et al.* (1955). Tidal volume was recorded either by means of a spirometer, the movement of which was transmitted to a potentiometer, or by electrical integration of a pneumotachographic tracing. The compliance of the lungs was measured from the pressure difference at the points of zero air flow and

TABLE I

CLINICAL AND PHYSIOLOGICAL DATA IN 27 PATIENTS WITH PULMONARY HYPERTENSION

Number	Sex	Age in years	Grade of dyspnœa	Pulmonary artery pressure Systolic diastolic and mean in mm. Hg		Mean wedge pressure in mm. Hg	Pulmonary flow in l./min.	Pulmonary vascular resistance in units	Systemic arterial pressure Systolic diastolic and mean in mm. Hg		Systemic flow in l./min.	Diagnosis and remarks
1	F	16	2A	120/75	95	1	5·1	18	115/75	90	5·1	A.S.D.
2	F	27	2B	95/0*	—	—	—	—	—	—	—	A.S.D. (catheter incomplete)
3	F	30	2B	88/50	65	5	4·6	13	120/85	95	2·7	A.S.D. (L.A. 92%)
4	F	31	2B	125/75	90	—	2·1	40†	115/75	85	4·9	A.S.D.
5	F	34	2A	90/35	52	12	2·6	15	120/75	96	2·6	A.S.D.
6	F	40	2B	75/32	49	—	2·8	17†	95/65	75	3·1	A.S.D. (P.V. 87%)
7	F	54	3	110/5*	—	—	3·5	—	107/55	72	3·9	A.S.D. (P.V. 91%) Asthma
8	F	27	2A	75/25	40	0	3·0	13	110/80	85	2·8	A.S.D. ? Ostium primum
9	F	21	2A	120/60	80	0	5·3	15	120/70	85	5·3	V.S.D.
10	F	26	2B	105/65	80	1	3·0	26	105/70	80	4·1	V.S.D.
11	F	40	3	115/50	70	−4	3·2	23	115/60	72	3·6	V.S.D. (P.V. 94%)
12	F	57	3	145/55	90	0	1·3	69	160/100	120	2·5	V.S.D.
13	F	45	2B	110/60	80	—	2·0	25‡	110/60	80	2·7	M.S. M.I.
14	F	45	3	100/35	65	25	1·4	24	110/75	85	1·7	M.S.
15	F	48	2B	90/45	60	20	2·2	18	130/80	95	2·7	M.S.
16	F	20	2B	105/60	75	—	1·8	42†	120/80	95	2·4	Idiopathic
17	F	64	2B	80/24	40	4	1·5	24	120/65	85	2·4	Idiopathic
18	F	57	2B	105/30	55	—	3·3	15†	115/30	75	3·3	Cor pulmonale Pulmonary fibrosis
19	M	45	1	75/25	40	1	4·5	9	125/65	90	5·4	A.S.D.
20	M	32	2A	105/60	80	—	2·5	32†	105/60	80	3·0	A.S.D. ? Ostium primum
21	M	36	2A	120/60	80	—	3·0	26†	120/60	80	6·0	V.S.D.+P.D.A.
22	M	43	2B	115/65	80	—	2·5	32†	115/65	80	4·5	P.D.A. Bronchitis
23	M	46	2B	125/90	105	8	3·7	26	125/75	95	4·1	P.D.A.
24	M	26	2A	110/70	80	30	3·3	15	90/65	75	4·5	M.S.
25	M	39	2A	70/35	55	18	3·6	10	100/65	75	4·0	M.I. M.S.
26	M	23	1	65/25	45	—	4·4	10†	125/75	90	4·8	Idiopathic
27	M	46	2B	120/75	90	—	3·4	26†	—	—	—	Idiopathic

* Right ventricular pressure. † Assuming wedge pressure zero. ‡ Assuming wedge pressure 30.

the tidal volume. The respiratory resistance during inspiration was measured from the non-elastic pressure difference at the mid-point of inspiration and the rate of air flow at the same instant. Both values were expressed as the average for five breaths.

In 11 patients the diffusing capacity of the lungs for carbon monoxide (Dco) was measured by the method described by Bates *et al.* (1955). In these patients the lung volume (F.R.C.) and "mixing efficiency" were measured using the closed circuit helium method (Bates and Christie, 1950). In a number of patients, the oxygen saturation was measured with an ear oximeter at rest and after exercise. The accuracy of the instrument was checked by comparing oximetric readings with simultaneous arterial samples analysed by Haldane's method. A graph of the oximetric reading plotted against the oxygen saturation of arterial samples is shown in Fig. 1. (p. 400).

RESULTS

The values for lung compliance and inspiratory resistance at rest and after exercise are shown in Table II, together with the oxygen saturation measured with the oximeter. Although there was

TABLE II

THE MECHANICAL PROPERTIES OF THE LUNGS IN 27 PATIENTS WITH PULMONARY HYPERTENSION

	Rest					Exercise				
Number	Compliance in l/cm. H_2O	Inspiratory resistance in cm. H_2O/l/sec.	Minute volume in litres	Oxygen saturation % (oximeter)	Rate of change of saturation on 100% O_2 in %/min.	Grade of exercise in number of flights of stairs	Compliance in l/cm. H_2O	Inspiratory resistance in cm. H_2O/l/sec.	Minute volume in litres	Oxygen saturation % (oximeter)
1	0·184	2·7	34·0	91	—	3	0·105	1·1	51·3	80
2	0·069	4·5	9·7	85	4·3	<1	0·073	4·2	22·7	—
3	0·076	0·7	19·0	95	—	1	0·074	1·0	27·2	95
4	0·139	3·4	13·1	82	3·5	1	0·076	3·5	13·6	82
5	0·047	9·1	13·1	92	—	4	0·133	4·6	30·0	—
6	0·108	2·2	9·8	89	4·0	<1	0·134	3·7	36·6	—
7	0·256	5·8	11·9	84	27·0	<1	0·214	4·9	20·7	—
8	0·155	5·7	9·6	93	—	2	0·178	1·3	33·5	80
9	0·088	4·9	11·1	87	—	2	0·097	5·8	17·0	80
10	0·141	5·6	10·8	90	—	2	0·096	4·2	18·1	75
11	0·114	2·4	16·4	90	—	—	—	—	—	—
12	0·077	4·8	8·6	85	3·8	<1	0·062	2·9	14·9	—
13	0·022	10·0	5·7	86	1·4	2	0·044	6·6	8·5	88
14	0·054	6·9	9·0	87	20·0	<1	0·097	8·2	12·3	87
15	0·162	—	6·1	—	—	2	0·057	5·6	11·1	—
16	0·160	1·0	17·9	87	—	2	0·095	0·9	43·8	87
17	0·085	9·7	9·7	92	—	2	0·076	2·4	13·4	—
18	0·051	14·0	11·2	87	14·6	1	0·051	12·1	12·2	81
Mean	0·114	5·5	—	—	—	—	0·098	4·3	—	—
Normal	0·13	2·8	—	—	—	—	0·13	2·3	—	—
Range	0·09–0·18	1·5–4·8	—	—	—	—	0·09–0·18	2·0–3·0	—	—
19	0·115	2·2	16·1	87	3·0	4	0·127	1·5	38·1	—
20	0·097	3·8	6·7	75	1·7	2	0·128	2·1	20·7	—
21	0·107	4·2	12·1	80	3·6	4	0·125	2·3	33·0	76
22	0·034	13·7	5·5	96	—	3	0·036	7·9	10·3	93
23	0·217	3·2	20·3	89	—	—	—	—	—	87
24	0·081	5·1	27·9	90	7·5	2	0·072	4·5	26·5	89
25	0·092	2·3	17·0	90	—	2	0·077	4·3	25·0	90
26	0·173	1·0	11·1	—	—	4	0·086	2·1	16·6	—
27	0·118	4·3	15·8	95	—	2	0·128	3·7	29·6	90
Mean	0·115	4·4	—	—	—	—	0·097	3·6	—	—
Normal	0·19	2·0	—	—	—	—	0·22	1·4	—	—
Range	0·14–0·33	0·7–3·5	—	—	—	—	0·12–0·39	0·6–2·2	—	—

considerable variation from patient to patient, the values for compliance tended to be less, and for inspiratory resistance greater than normal. As would be expected, lung compliance was reduced in the patients with mitral valve disease (Marshall *et al.*, 1954; Hayward and Knott, 1955), and also in the patient with pulmonary fibrosis (Case 18) in whom the inspiratory resistance was also raised. In two patients with congenital heart disease, in whom there was a history of associated lung disease (Cases 7 and 22), the mechanical properties of the lungs were also grossly abnormal. In Case 7, with a long history of asthma, there was a high compliance and a high inspiratory resistance, while in Case 22 with a long history of winter bronchitis, the compliance was greatly reduced and the inspiratory resistance high. Further evidence of associated lung disease was obtained

from the measurement of the rate of change of oxygen saturation when the patient breathed 100 per cent oxygen. In Cases 7 and 18 the rate of change of saturation was 27 per cent and 15 per cent per minute, indicating that the reduction in arterial saturation was due to impaired diffusion in the lungs rather than to a right-to-left shunt: this will be referred to later when the diffusing capacity is considered. The third patient, in whom the arterial oxygen saturation changed rapidly with 100 per cent oxygen (Case 14), had mitral stenosis, and it is presumed that diffusion in the lungs was impaired in this patient although the diffusing capacity was not measured.

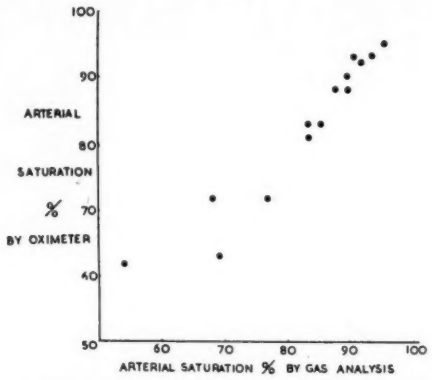


FIG. 1.—Comparison of oxygen saturation of arterial samples with oximeter reading in 13 patients.

The values for lung volume, mixing efficiency, and Dco at rest and during exercise are shown in Table III. The lung volumes were within normal limits and mixing was normal in all except the two patients with associated lung disease (Cases 7 and 18). The values for the diffusing capacity were generally less than normal and, as the values obtained in normal subjects vary with lung volume, the results have been shown in Fig. 2 plotted against the lung volume (F.R.C.). The normal range is derived from the results using this method in young normal subjects (Bates *et al.*, 1955). It will be seen that Cases 7 and 18 with associated lung disease showed lower values than the rest of the group, confirming the suggestion, made from the measurement of the rate of change of arterial saturation on 100 per cent oxygen, that diffusion was impaired in these two patients. In the other 9 patients the diffusing capacity was lower than expected on the basis of lung volume and did not increase normally on effort. In only one (Case 1), the youngest patient with congenital heart disease studied, was the Dco within normal limits.

The ventilation equivalent for oxygen (O_2/V) in ml. O_2/litre ventilation was measured in 9 patients during exercise and found to be low, indicating a greater ventilation than normal for a given oxygen consumption. In the patients in whom oxygen consumption was not measured, a lowered ventilation equivalent could only be inferred from the high levels of ventilation required for relatively mild exercise. In Case 26, a young man in whom the diagnosis of primary pulmonary hypertension was made following the discovery of a dilated pulmonary artery on mass radiography, the ventilation equivalent was normal. His oxygen consumption on moderately severe exercise was 1550 ml./min. with a ventilation equivalent of 43 ml. O_2/l. ventilation.

DISCUSSION

These results indicate that the disturbance of pulmonary function in patients with pulmonary hypertension varies considerably. In deciding how much of the abnormality is due to pulmonary hypertension and how much to associated conditions, it is important to consider the results in those patients in whom there was no associated lung disease and no mitral valve disease, two con-

TABLE III

THE DIFFUSING CAPACITY FOR CARBON MONOXIDE IN 11 PATIENTS WITH PULMONARY HYPERTENSION

					Exercise				
Number	Vital capacity in litres	Functional residual capacity in litres	Mixing efficiency %	D.CO at rest in ml/min./mm. Hg	Treadmill speed in m.p.h.	Minute volume in litres	Oxygen consumption ml./min.	Ventilation equivalent O_2V in ml./l.	Exercise D.CO in ml./min./mm. Hg
1	2·57	2·29	71	15·0	2¼	29·1	737	25	20·0
2	1·65	2·11	66	6·4	2¼	14·7	350	24	7·6
3	2·16	2·2	58	10·0	2¼	19·6	510	26	15·4
4	2·47	3·34	102	9·6	2¼	23·1	395	17	13·3
5	2·77	2·7	89	11·2	2	22·3	652	29	11·4
7	2·04	3·03	45	7·9	—	—	—	—	—
8	3·29	3·77	80	12·8	1¾	30·3	571	19	16·0
16	2·03	2·47	68	10·0	1¾	31·2	549	18	14·8
18	1·50	3·29	31	4·5	1¾	12·5	280	22	7·5
21	4·27	3·28	78	17·1	1	22·3	665	30	19·1
23	3·44	5·31	83	12·4	½	20·4	770	38	21·0

ditions that are known to affect the mechanical properties of the lungs. The general picture that emerges when such cases are excluded is that pulmonary hypertension is associated with a normal or reduced compliance of the lungs, a normal or slightly raised inspiratory resistance, and a low diffusing capacity which does not increase normally on exercise. That these changes are not the direct result of a raised pulmonary vascular resistance is shown in Case 26, in which pulmonary function was normal in the presence of a pulmonary vascular resistance of 10 units (800 dyne sec./cm.$^{-5}$). Any attempt to explain the variable impairment in pulmonary function found in patients with pulmonary hypertension must be speculative, but it seems possible that pulmonary vascular disease with local thrombosis or embolism in different parts of the lungs could produce changes that would vary from patient to patient. If this were the case, the impairment of pulmonary function might well depend on the duration of the pulmonary hypertension. Such a concept is supported by the fact that among the patients with congenital heart disease, the disturbance of

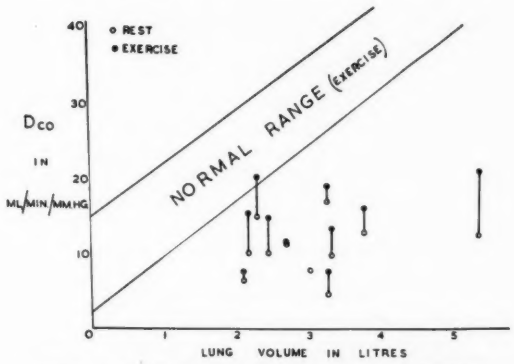


FIG. 2.—The relationship between the diffusing capacity for carbon monoxide and lung volume in 11 patients with pulmonary hypertension.

pulmonary function was least in the youngest patient (Case 1), and also that, in Case 26, in which primary pulmonary hypertension was diagnosed in a pre-symptomatic stage, pulmonary function was normal. The exact mechanism by which thrombosis or embolism of the pulmonary arterial tree could lead to a reduction in lung compliance and an increase in respiratory resistance is not clear. It has, however, been shown by Doyle *et al.* (1957) that the pulmonary vascular bed is reduced in patients with pulmonary hypertension and congenital heart disease, and such changes could well account for the reduction in diffusing capacity by reducing the surface area available for gas exchange. It would not then be necessary to postulate any abnormality of the alveolar membrane in such patients. In this connection it should be stressed that the measurement of the diffusing capacity with carbon monoxide measures the overall process of diffusion and is influenced by inequality of ventilation, increased dead space effect, and venous admixture, as well as by any abnormality of the pulmonary membrane itself.

As has been shown, hyperventilation was common in the patients with pulmonary hypertension studied. In those patients with congenital heart disease and a right-to-left shunt, in whom the arterial saturation fell on exercise, hyperventilation would be expected to occur as a result of the fall in arterial oxygen tension and rise in arterial pCO_2 associated with increased shunting of venous blood into the systemic circulation on exercise. Some other factor must be invoked to explain the hyperventilation seen in patients with no shunt. The clearest example of this was seen in Case 16, a girl with primary pulmonary hypertension in whom the ventilation equivalent was 18 ml. O_2/l. This hyperventilation was not abolished by oxygen and the stimulus for it is unknown. That it is not directly related to the increased pulmonary vascular resistance is shown by the findings in Case 26 in which a raised pulmonary vascular resistance due to primary pulmonary hypertension was associated with a normal ventilation equivalent. Further work is needed to explain the nature of the ventilatory stimulus in such patients and to explore the suggestion that it may be related to limitation of the cardiac output.

Dyspnœa was the symptom that limited exercise performance in all the patients studied, and it appears that several factors may be responsible for this. Firstly, impairment of the mechanical properties of the lungs must result in an increase in the oxygen cost of breathing; secondly, hyperventilation due either to arterial oxygen unsaturation on effort or to some unknown stimulus must increase the ventilatory requirements for a given grade of exercise; thirdly, the restricted blood flow through the lungs on exercise must limit transport of oxygen to the tissues.

Summary

The mechanical properties and diffusing capacity of the lungs have been measured at rest and on exercise in patients with pulmonary hypertension.

There was no direct relationship between the level of the pulmonary vascular resistance and the degree of disturbance of pulmonary function, which ranged from zero to considerable. In general, patients with pulmonary hypertension showed a variable reduction in lung compliance, diffusing capacity, and ventilation equivalent, and a slight increase in inspiratory resistance.

It is suggested that while pulmonary hypertension *per se* has no effect on pulmonary function, changes in lung compliance, resistance, and diffusing capacity may result from associated lung disease, mitral valve disease, or the effects of thrombosis or embolism of the pulmonary arterial bed.

We wish to thank the physicians of the National Heart Hospital for allowing us to study their patients.

References

Bates, D. V., Boucot, N., and Dormer, A. E. (1955). *J. Physiol.*, **129**, 237.
—— and Christie, R. V. (1950). *Clin. Sci.*, **9**, 17.
Doyle, A. E., Goodwin, J. F., Harrison, C. V., and Steiner, R. E. (1957). *Brit. Heart J.*, **19**, 353.
Hayward, G. W., and Knott, J. M. S. (1955). *Brit. Heart J.*, **17**, 303.
Marshall, R., McIlroy, M. B., and Christie, R. V. (1954). *Clin. Sci.*, **13**, 137.
Mead, J., McIlroy, M. B., Selverstone, N. J., and Kriete, B. C. (1955). *J. app. Physiol.*, **7**, 491.

THE RIGHT VENTRICLE AND THE SMALL PULMONARY ARTERIES IN COALWORKERS

BY

ARTHUR J. THOMAS AND W. R. L. JAMES

From Llandough Hospital (United Cardiff Hospitals) and the Department of Pathology, Welsh National School of Medicine

Received November 27, 1957

In previous work (Thomas, 1951; James and Thomas, 1956), we have been made aware of some problems of pulmonary heart disease that needed further elucidation. Further consideration of the method of assessment of right ventricular hypertrophy and its relation to emphysema and pneumoconiosis when present, separately or together, was needed. Jaffe (1934), referred to the lesion of pneumoconiosis as including obliterative changes in the branches of the pulmonary artery. Other workers (Gough, 1952; Wells, 1954; James and Thomas, 1956), have referred to the presence of arterial lesions in the vessels of the lungs in pneumoconiosis. It seemed important to examine the relationship of these vascular changes to the right ventricular hypertrophy. The nature of the changes in the vessels is also in question. Pulmonary thrombosis has been regarded as a relatively rare happening, but we have found that in pulmonary heart disease, especially in coalworkers, it is much commoner than is thought. Other workers have seen differing kinds of arterial lesions in the lungs in other forms of pulmonary hypertension (McKeown, 1952; Wade and Ball, 1957), and it seemed important to try and assess the nature of the change in pneumoconiosis. Heart failure and lung disease has been reviewed by Hecht (1956), and from this review it is clear that forms of heart failure can differ in different pulmonary diseases.

Material and Method

The lungs and hearts from 71 necropsies on coalworkers were examined. The cases chosen were those likely to show right ventricular hypertrophy due to pulmonary disease.

The hearts were examined at necropsy and then fixed and re-examined by dissection so as to record the left and right ventricular weights. The ventricles were separated through the septum by the method of Hermann and Wilson (1922) and weighed. The free walls of the ventricles were then separated from the attached septal portions and the parts weighed separately. The thickness of the ventricular walls near the base of the heart had been measured in routine fashion at necropsy. There was thus available total heart weight, ventricular wall thickness as assessed at necropsy, ventricular weights including the share of the septum, free walls of both ventricles, and the separated right and left portions of the septum.

At necropsy one of us (W.R.L.J.) assumed responsibility for the preparation and examination of the lung specimens. One of the lungs was cut at that time and examined naked-eye before fixation. The other was perfused with formol-sodium acetate solution through the bronchus and allowed to fix in a distended state for one or more days. From each lung, blocks were taken for microscopic study. Some pieces were cut from areas of massive fibrosis and others from areas affected by simple pneumoconiosis only. The number of pieces of lung tissue examined varied from case to case, the minimum being 8 and the maximum 17. The sections obtained were stained with hæmalum and eosin, and studied microscopically with special reference to the state of the pulmonary arteries. From the lung that was perfused at necropsy, a whole lung section was made by the technique of Gough and Wentworth.

In studying the microscopic preparations, attention was directed mainly to the following branches of the pulmonary arteries as classified by Brenner (1935): (1) muscular arteries with external diameters ranging from 100μ to 1000μ, and (2) arterioles with external diameters usually less than 100μ. One of us (W.R.L.J.) subjectively assessed the severity of the lesions in these vessels as slight, moderate, or severe, on the basis of the examination of all the microscopic preparations available in each case. The other (A.J.T.), independently studied the heart and the relationship between the findings is shown (Fig. 1).

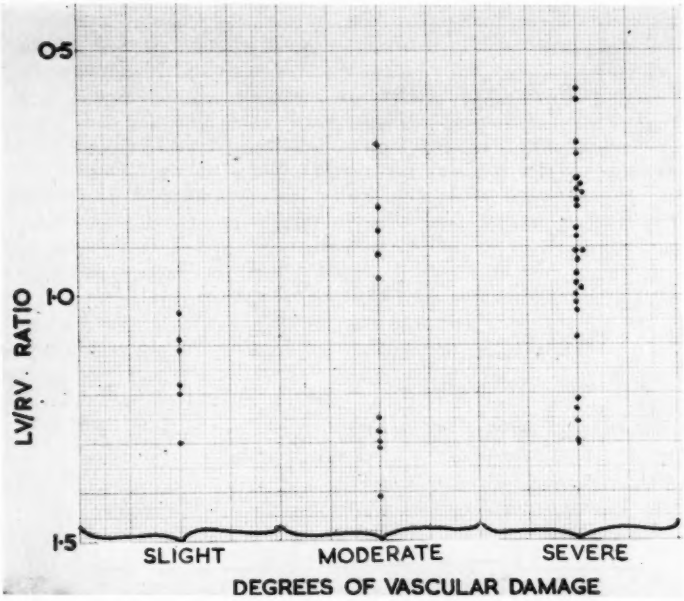


FIG. 1.—The relationship of the degrees of right ventricular hypertrophy and of severity of changes in the small pulmonary arteries.

As a result of the examination of the coronary arteries and the myocardium in detail it was necessary to discard from the pulmonary study 23 cases, because 22 had coronary heart disease of such severe degree as to affect decisions on cardiac pathology and one had aortic stenosis. This figure of 34 per cent of severe coronary heart disease is of the greatest interest, as we have pointed out elsewhere that on all occasions when we study coalworkers, we find a high incidence of coronary heart disease of this order. The detailed findings in the rejected cases will be described in a separate communication.

There remained 48 cases to be analysed in relation to the character and extent of the pulmonary disease and the degree of right ventricular hypertrophy.

RESULTS

Assessment of Ventricular Hypertrophy. The correlation of the LV/RV ratio of the dissected free ventricular walls with the LV/RV ratio of the ventricles when separated through the septum was close. The former is an easier method of determining right ventricular hypertrophy or preponderance.

In right ventricular hypertrophy we have noted large muscle columns arising from the right side of the septum and clearly part of the hypertrophy of the right side of the septum. It is clear that, when considering right ventricular hypertrophy alone, the total septal weight cannot be added to the weight of the left ventricle, for the error produced may be significant and may mask the slighter degrees of right ventricular preponderance, especially in small hearts (Fig. 2).

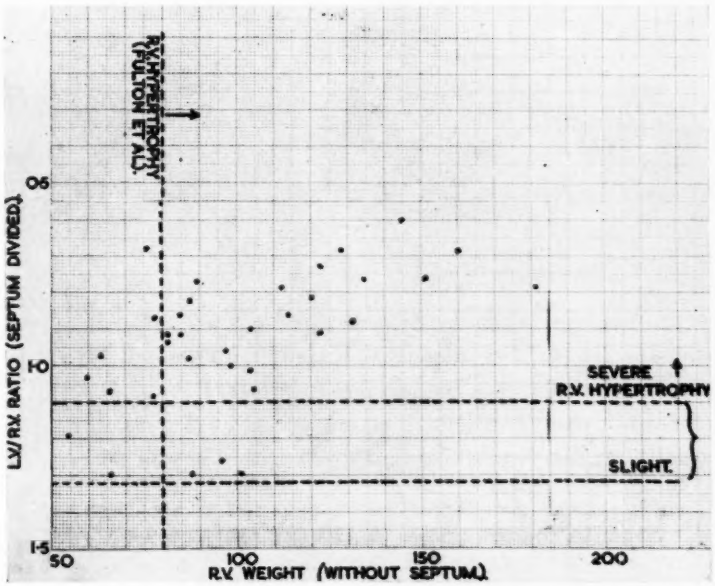


FIG. 2.—The correlation of the LV/RV ratio with the right ventricular weight as a criterion of hypertrophy. If a free right ventricular wall weight of over 80 g. is required for hypertrophy, then right ventricular preponderance in some small hearts will not be detected.

When we considered the thicknesses of the right ventricular and left ventricular walls we found that there was good correlation with LV/RV ratios over the middle ranges of right ventricular hypertrophy, but in small hearts with right ventricular wall thicknesses of 3 or 4 mm., the LV/RV ratio often showed right ventricular preponderance (Fig. 3), which would not be detected by simple measurement of right ventricular thickness. In several such cases the chronic venous congestion of heart failure was present. The right ventricular wall thickness of 5 mm. is an equivocal measure and may or may not be a true indication of right ventricular hypertrophy (Fig. 3), but if it is above 5 mm. it always correlates well with true hypertrophy.

The form of the hypertrophy is not consistent; in some cases trabecular hypertrophy is striking but in others there is a more compact hypertrophy of the whole wall. It may be that the degree of dilatation decides the prominence of the trabeculæ.

The Pulmonary Disease and Vascular Changes. In the areas of lung showing only simple pneumoconiosis normal vessels were the rule. On examining the sections prepared from areas of massive fibrosis the tissue was relatively avascular in comparison with the rest of the lung and almost all vessels that had survived were abnormal. No examples of frank vascular necrosis were found, but in most vessels there was distortion, degeneration, and evidence of reduction of the lumen by disease of the vessel wall or thrombosis.

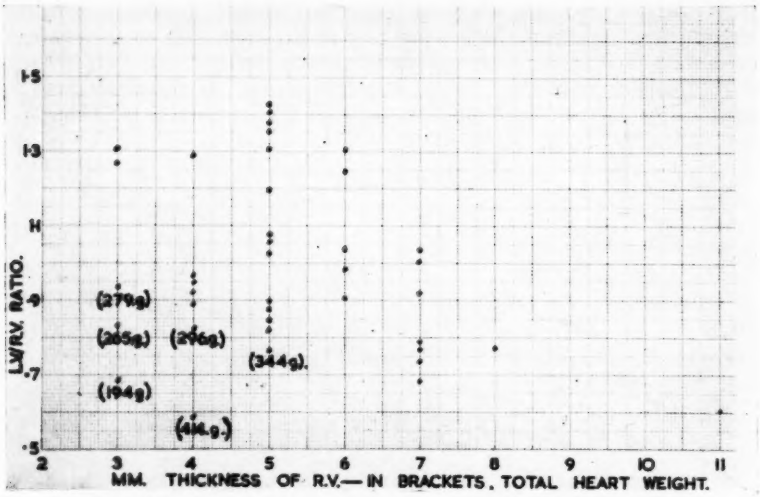


FIG. 3.—The distribution of right ventricular hypertrophy determined by LV/RV ratio and by thickness of right ventricular wall. It is noted that small hearts, and also one large but dilated heart, tend to have a relatively thin right ventricular wall.

In many vessels there was gross disproportion between the area of the vessel wall section and the area of the lumen, with fibrous distortion of the vessel wall (Fig. 4), and in many the wall was infiltrated with scanty plasma cells and lymphocytes and numerous dust-laden macrophages, and there were multiple lumina due to recanalized thrombi (Fig. 5). Sometimes compression of adjacent structures such as bronchi indicated that vascular swelling had occurred (Fig. 6).

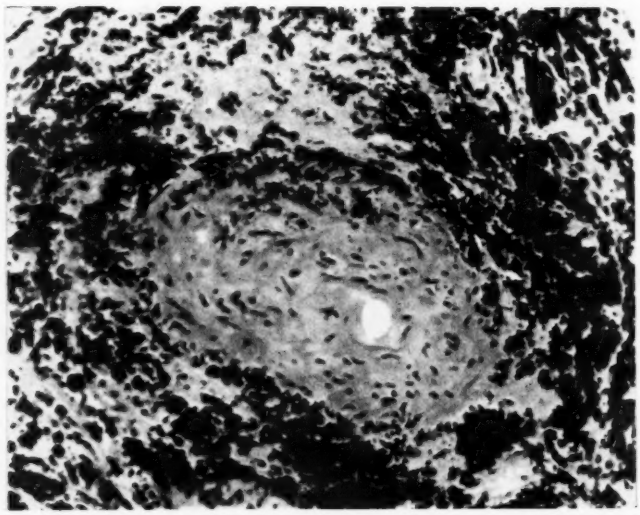


FIG. 4.—(×180). A vessel of muscular artery size in an area of massive dust fibrosis. The wall is grossly fibrosed and thickened and few muscle cells have survived. (Age 48 years, LV/RV ratio, 0·79, R.V. weight 132 g.)

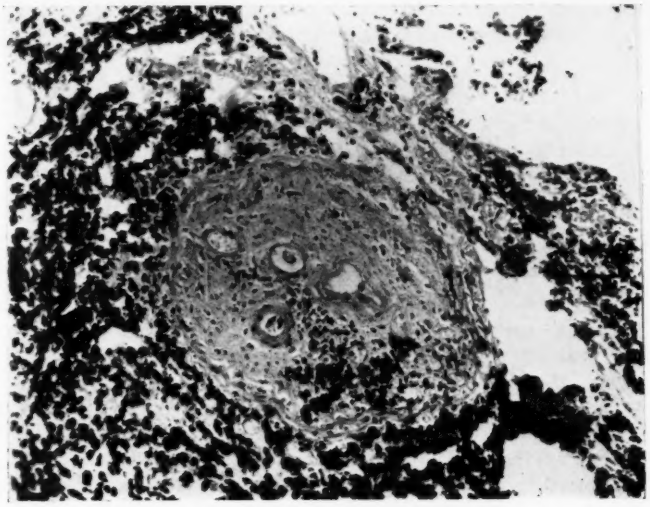


FIG. 5.—(×120). The wall of the vessel is thick and consists mainly of fibrous tissue infiltrated by dust laden macrophages and chronic inflammatory cells. The four lumina indicate recanalization of old thrombus. (Age 52 years, LV/RV ratio 0·91, R.V. weight 112 g.)

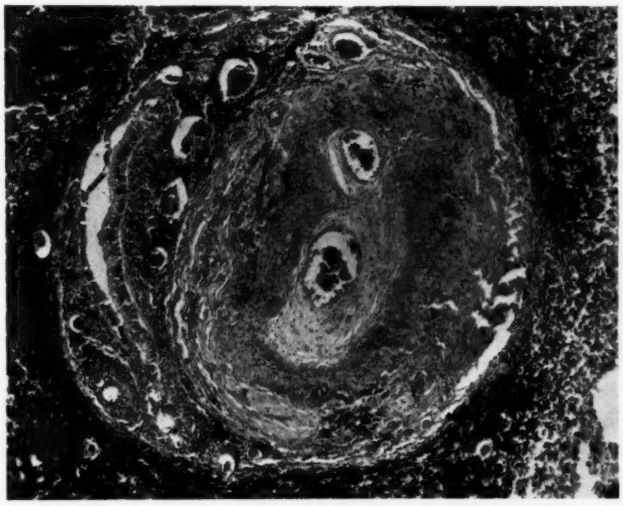


FIG. 6.—(×50). The vessel wall is fibrosed and the lumen is reduced by an organized recanalized thrombus. The lumen of the adjacent bronchiole is reduced to a narrow slit, apparently as a result of the enlargement of the artery. The electrocardiogram of this case shows the right ventricular hypertrophy. (Age 35 years, LV/RV ratio 0·6, R.V. weight 170 g.)

In 8 of the 48 cases examined the vascular lesions were graded as slight, in 12 as moderate, and in 28 as severe. The relationship between the severity of the lesions and the LV/RV ratio is shown (Fig. 1).

The Right Ventricular Changes. An analysis based on the state of the right ventricle showed severe hypertrophy in 31, slight hypertrophy in 11, and none in 6. The 31 with severe hypertrophy had an LV/RV ratio below 1·1. The mean age of the 31 patients was 62 years (35 to 73 years), the mean heart weight was 324 g. (194–545 g.), and the mean weight of the right ventricle was 127 g. (range 70–220 g.).

Of the 31 with an LV/RV ratio below 1·1, there were 9 whose right ventricular wall thickness was 3 or 4 mm. and in 7 of them the hearts were small. In 4 of these, pulmonary tuberculosis had been demonstrated.

Another sub-division of great importance in the 31 cases was the group of 9 with progressive massive fibrosis and little or no other pulmonary disease. The mean age of the 9 patients was 52 years (35 to 63 years), the mean ratio of LV/RV was 0·88, the right ventricular mean weight was 139 g. (77–220 g.), and the right ventricular thickness was considerable in all except two, one of whom had tuberculosis.

When we tried to express the extent of the progressive massive fibrosis as a factor, using the sum of the maximum diameters in centimetres of the massive lesions in both lungs, we found a mean "PMF" factor of 19 in the cases of severe right ventricular hypertrophy. This would have been higher but for two instances with readings of ten. There was one unusual case without massive fibrosis, but with gross arterial changes in many small fibrous lesions resulting in hypertrophy.

There was pulmonary thrombosis of macroscopic degree in 7 of the 31 cases and it was not all formed just before death. Histological evidence of thrombus organization was frequent in medium sized arteries. The occurrence of thrombosis seemed sometimes to have caused a recognizable clinical episode.

Chronic venous congestion of the liver and spleen was almost always present at necropsy, although not always recognized clinically. A palpable tender liver margin is a good early sign of pulmonary heart failure in these cases (Thomas, 1948). Electrocardiograms taken at a late stage of the illness always showed an indication of pulmonary heart disease, usually pulmonary P waves, vertical heart pattern, and R–S complexes in V6. In many there was unequivocal evidence of right ventricular hypertrophy.

Slight Right Ventricular Hypertrophy. This group with LV/RV ratio 1·1 to 1·3 inclusive comprised 11 patients whose mean age was 69 years (range 51–81), an older group than those with severe right ventricular hypertrophy. The mean heart weight was 278 g. (range 207–339 g.), and the mean right ventricular weight was 93 g. (range 67–125 g.). So although they were a slightly older group with rather smaller hearts, they still had evidence of the presence of some right ventricular hypertrophy. It is proper to take this group by their LV/RV ratio because, when the thicknesses are taken, one finds that there are right ventricles of 3 mm. and 4 mm. in patients who had chronic venous congestion and died in right heart failure.

In those with slight right ventricular hypertrophy three had progressive massive fibrosis but no emphysema. In this group as a whole the vascular lesions were much less intense than in those with severe right ventricular hypertrophy.

Absence of Hypertrophy. There remained a small group of 6 cases with LV/RV ratio over 1·3 which was incompatible with isolated right ventricular hypertrophy, though this was expected at necropsy. Their mean age was 60 years, but ranged from 39 years to 81 years, and their mean heart weight was 325 g. (235–455 g.). The average progressive massive fibrosis factor was 12.

The vascular lesions were slight in one, moderate in four, and severe in one. This last case should have shown right ventricular hypertrophy; one possible explanation for his not doing so was protection by a long period of reduced physical activity. Tuberculosis was present in two cases and rheumatoid arthritis in one.

Discussion

A study of the pulmonary blood vessels in coalworkers' lungs has led us to suggest, as have others previously (Jaffe, 1934; Gough, 1952), that the change in the medium and small arteries is responsible for the increased right ventricular work resulting in hypertrophy. The changes in the vessels are fibrosis and thickening of the muscular wall, with disappearance of the muscle fibres and reduction of the lumen due to intimal thickening or fibrosis. There is a recognizably high incidence of thrombosis in the large and medium arteries and this may well happen in the small vessels too.

This type of pulmonary disease is commonly a mixture of massive fibrosis, emphysema, and "chronic bronchitis". By identifying 9 cases of massive fibrosis without emphysema but with severe arterial lesions and right ventricular hypertrophy, we have shown the part that such fibrosis can play in producing right ventricular hypertrophy. Also it becomes evident that smaller areas of lung fibrosis, with lesser degrees of arterial change, are as a rule accompanied by slighter grades of right ventricular hypertrophy.

The total heart weight is often low, sometimes in association with recognized tuberculosis, and in such cases it becomes necessary to weigh the right and left ventricles by some method, to identify the relative right ventricular hypertrophy. The right ventricular wall thickness can be misleading in these circumstances. There is usually ample evidence of chronic venous congestion in the liver and spleen to support the diagnosis of pulmonary heart disease.

Some points in this study suggest that emphysema and bronchitis hasten the development of the pulmonary heart disease and certainly recurrent exacerbation of infection does so. Of equal interest is some evidence that reduction of physical activity over a long period delays the final episode of heart failure, and may also slow the rate of hypertrophy of the right ventricle. Conversely, persistence in physical activity, as in the younger age group, increases the rate of development and degree of hypertrophy of the right ventricle. This can be explained by the presence of the inelastic or obstructive pulmonary vascular state, as there is a stage when the pulmonary artery pressure is normal at rest, but is raised progressively on effort. This causes an increase in right ventricular work and we think that, once the right ventricle has to work harder to maintain the pulmonary flow on slight exercise, then an irreversible sequence of events has started.

Summary

The lungs and hearts from 71 necropsies in coalworkers have been examined and, after rejecting 23 cases because of coronary heart disease in 22 and aortic stenosis in 1, 48 have been analysed in relation to the right ventricular hypertrophy and the extent of changes in the smaller pulmonary arteries. The lungs were studied macroscopically and by microscopic preparations.

It was found that the LV/RV ratio obtained by full dissection correlated well with the LV/RV ratio obtained by weighing the free walls taken off close to the septum. Thicknesses of the right ventricle above 5 mm. correlated well with right ventricular hypertrophy, but in some cases values of 3 mm. and 4 mm. were recorded in hearts shown by dissection to have right ventricular preponderance. The latter were usually small hearts, but the accompanying severe chronic venous congestion of liver and spleen supported their classification as pulmonary heart disease.

Lungs showing simple pneumoconiosis as a rule had normal vessels. Areas of progressive massive fibrosis showed relatively avascular regions with all surviving vessels around them abnormal.

Severe vascular lesions were present with moderate or severe right ventricular hypertrophy. In

9 cases massive fibrosis with vascular change was the only reason found for right ventricular hypertrophy. The general correlation suggests that the changes in the smaller pulmonary arteries and the arterioles are responsible for the right ventricular hypertrophy.

We are grateful to Professor J. Gough of the Department of Pathology, Welsh National School of Medicine for his help and advice, and to Dr. J. C. Gilson, Director, and Dr. Rivers, Pathologist, Pneumoconiosis Research Unit (MRC) for access to records and permission to study their cases. We would like to thank Mr. Leighton Williams, A.I.B.P., and Mr. Napper for the photographic illustrations.

References

Brenner, O. (1935). *Arch. intern. Med.*, **56**, 976.
Fulton, R. M., Hutchinson, E. C., and Jones, A. M. (1952). *Brit. Heart J.*, **14**, 413.
Gough, J. (1952). A paper read before the Fourth Conference of the McIntyre Research Foundation on Silicosis, Noranda, Quebec, January, 1952.
Hecht, H. H. (1956). *Circulation*, **14**, 265.
Hermann, G. R., and Wilson, F. N. (1922). *Heart*, **9**, 91.
Jaffe, R. H. (1934). *Illinois med. J.*, **66**, 431.
James, W. R. L., and Thomas, A. J. (1956). *Brit. J. industr. Med.*, **13**, 24.
McKeown, F. (1952). *Brit. Heart J.*, **14**, 25.
Thomas, A. J. (1948). *Brit. Heart J.*, **10**, 282.
—— (1951). *Brit. Heart J.*, **13**, 1.
Wade, G., and Ball, J. (1957). *Quart. J. Med., N.S.*, **26**, 83.
Wells, A. L. (1954). *Brit. Heart J.*, **16**, 74.

CORONARY ARTERY CATHETERIZATION DURING THORACIC AORTOGRAPHY

BY

A. M. JOHNSON AND WILLIAM D. LOGAN

From the Cardiac Department, Guy's Hospital

Received December 20, 1957

Ever since the introduction of retrograde aortic catheterization for the purpose of radiological demonstration of the thoracic aorta and its branches, the importance of correct positioning of the catheter tip before injection of opaque material has been emphasized. Several workers have stated the optimal position as being a short distance above the aortic valve.

The importance of fluoroscopic demonstration that the tip lies free in the main aortic stream at this site was stressed by Pearl *et al.* (1950), who suggested as aids to correct positioning, the sensation of resistance to the catheter at the aortic valve and the fluoroscopic demonstration of buckling of the catheter when the valve is reached: they reported that the left ventricle might be entered at this time and mentioned that "a forceful systolic impulse" might be transmitted to the operator's hand along the catheter. Zimmerman *et al.* (1950), who performed retrograde aortic catheterization through the left ulnar artery, found it impossible to enter the left ventricle from the aorta in five normal subjects. By selecting patients with aortic regurgitation, however, they succeeded in eleven of them and obtained pressure records. One showed ventricular premature contractions, while another had runs of ventricular tachycardia: in both, sinus rhythm was restored "by moving the tip of the catheter." One patient, with rheumatic aortic and mitral disease, during the attempt to move the catheter into the left ventricle suddenly complained of substernal pain and developed ventricular fibrillation from which he died in fifteen minutes: it was thought probable that the catheter had occluded a coronary ostium.

Zimmerman *et al.* (1951) later reported left ventricular catheterization by the same technique, for the purpose of studying cavity potentials in the ventricle. Eight syphilitic and two hypertensive cases of aortic regurgitation were studied and in six of these the left ventricle was entered. The position of the tip of the catheter was determined by fluoroscopy, by the increase in voltage of the cardiogram when the catheter tip entered the cavity of the left ventricle, and by observing the form of the pressure curve. That the latter criterion may be grossly misleading is shown by the present report.

Brodén *et al.* (1949) pointed out how easily the catheter may "glide into one of the coronary arteries," as happened in one of their cases where the right coronary artery was entered and injected with opaque fluid without untoward effect except for slight tachycardia. Jönsson *et al.* (1951), discussing thoracic aortography for the demonstration of patent ductus arteriosus and coarctation, state that the catheter tip "may fasten in the orifice of one of the coronary arteries, with perhaps fatal results."

Helmsworth *et al.* (1950) reported their attempts at coronary arteriography in six patients, two of whom died following repeated injection of contrast medium. As DiGuglielmo and Guttadauro (1952) indicate in their monograph on coronary arteriography, such repeated injections constitute a series of periods of myocardial anoxia.

Pressure measurements during aortography may clearly be of value. When, for example, a catheter has been introduced into the aorta for the purpose of radiological demonstration of a persistent ductus, the ductus itself may be traversed during the manipulations and a record of pulmonary arterial pressure is then a useful and perhaps crucial piece of information. Johnson *et al.* (1957) in a recent assessment of the uses of thoracic aortography, point out that "in occasional instances hæmodynamic data with reference to the left ventricle may be obtained when the catheter tip slips easily into the left ventricle." This occurred in one of eighteen cases studied and left ventricular and aortic pressures were recorded. The propriety of attempting to enter the left ventricle in this way is seriously questioned in the light of the present case report. Thoracic aortography may now find widening application to the problems of coronary artery disease, and a recent report by Thal *et al.* (1957) illustrates this trend.

For these reasons we have felt it important to report a case in which, during aortography for demonstration or exclusion of a persistent ductus arteriosus in a girl with proven pulmonary stenosis, pressure records were misleading and were largely the cause of failure to recognize that the catheter had entered the right coronary artery. It is thought probable that the misleading nature of pressure waves obtainable in the coronary artery may not be widely recognized.

Case Report

A girl, aged ten, had undergone right heart catheterization two years before, which confirmed a clinical diagnosis of pulmonary valve stenosis with closed septa. Pressures were 80/4 mm. Hg in the right ventricle and 12/8 mm. in the pulmonary artery. Blood oxygen estimations, however, suggested the coexistence of persistent ductus arteriosus and it was decided to perform aortography to confirm or exclude this diagnosis.

Under general anæsthesia, a No. 7 Cournand catheter was introduced into the left brachial artery and advanced under fluoroscopic control. After a few passages down the descending aorta the catheter entered the ascending aorta and was advanced, without apparent resistance, to a point near the right cardiophrenic angle, well below the expected region of the aortic valve. Here an atrial wave form was observed on a pressure recording. Slow withdrawal of the catheter then resulted in a sudden change to ventricular wave form and finally a return to aortic pressure waves as observed on the inward passage (Fig. 1). The finding of these atrial and ventricular pressures suggested that the catheter had entered the left ventricle and left atrium or even, through a ventricular septal defect, the right ventricle and right atrium. In retrospect, it is obvious that the catheter position was incompatible with these suggestions, but at the time the sequence was repeated thrice by advancing and withdrawing the catheter and finally it was decided to inject 10 ml. of 70 per cent diaginol at the "atrial" site. During the subsequent catheter withdrawal the electrocardiogram, which had hitherto remained unchanged, showed bursts of rapid irregular idioventricular rhythm. This ceased when the catheter was withdrawn further, into the aorta, but there was now S–T depression in lead I, the monitored lead at the time. X-ray films taken showed dense filling of the right coronary artery with an intense blush, indicating capillary filling, in the area of myocardium supplied (Fig. 2A). After an interval of ten minutes the catheter tip was positioned about 3 cm. above the aortic valve and, with simultaneous carotid compression, 30 ml. of 70 per cent diaginol was injected rapidly. A satisfactory aortogram was obtained and, again, right coronary artery filling was seen (Fig. 2B). No ductus arteriosus was shown. There was a sinus tachycardia at a rate of 144 a minute, and marked S–T depression in leads I and aVL and S–T elevation in leads III and aVF.

Study of the pressure records showed that insertion of the catheter into the coronary artery was followed on the three occasions by a rise of aortic pressure. This returned to the initial normal level when the catheter, following the third withdrawal, was left free in the aorta for some minutes, but rose again when the catheter was finally reinserted and 10 ml. diaginol was injected. There was a further rise after the second injection which filled the right coronary artery from the aorta. The initial aortic pressure (from mid-thoracic level) was 135/71 mm., the final pressure 159/107 mm. Hg.

Subsequent cardiographic progress indicated posterior myocardial infarction (Fig. 3) and the clinical course was compatible with this. Though she experienced no pain and there was neither hypotension nor evidence of heart failure, she was febrile to 100·6 °F. on the next day, with gradual return to normal by the eighth day. Blood counts, previously normal, showed a leucocytosis of 13,200 (polymorphs, 72%) on the following day, and fell to a normal total count by the fourth day, though the polymorphs were still relatively increased at the tenth day. The E.S.R. (Westergren) rose to a peak of 25 mm. in one hour by the fifth day and returned to normal by the tenth day. Clinically, recovery appeared complete.

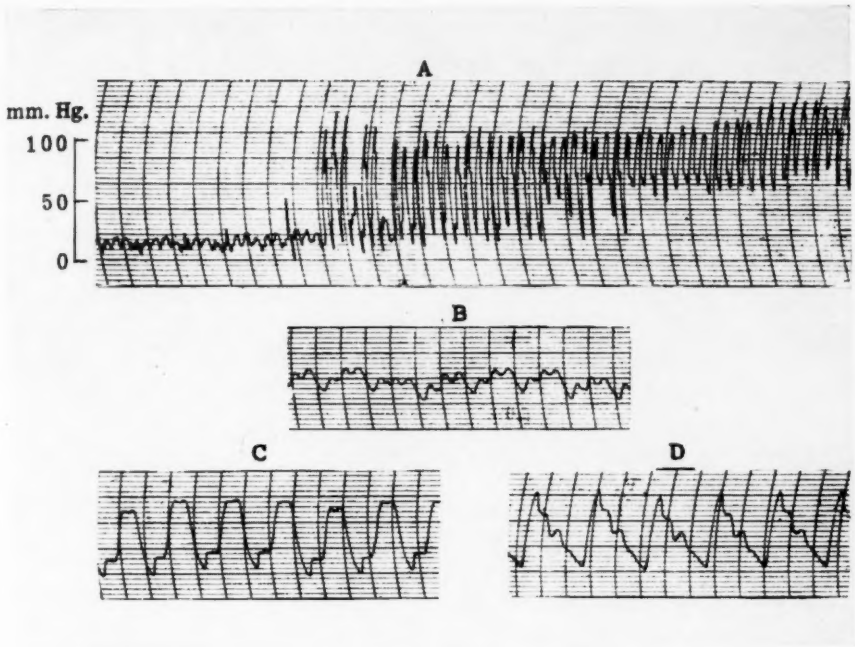


FIG. 1.—(A) Pressure record during withdrawal from wedge position in right coronary artery to aorta. (B), (C), and (D). "Atrial", "ventricular", and aortic wave forms respectively, at different sensitivity ranges.

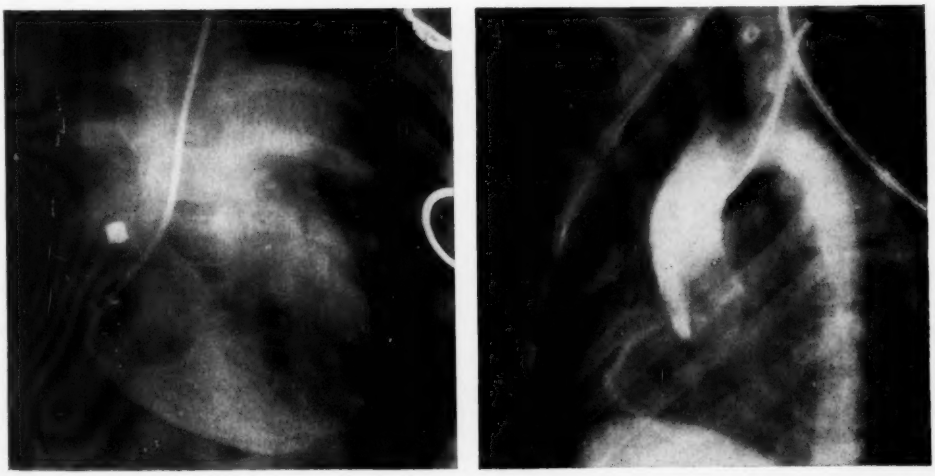


FIG. 2.—(A) Injection from catheter lying in the right coronary artery, showing dense concentration of opaque fluid in the area of myocardium supplied. (B) Injection into the ascending aorta, showing further filling of the right coronary artery.

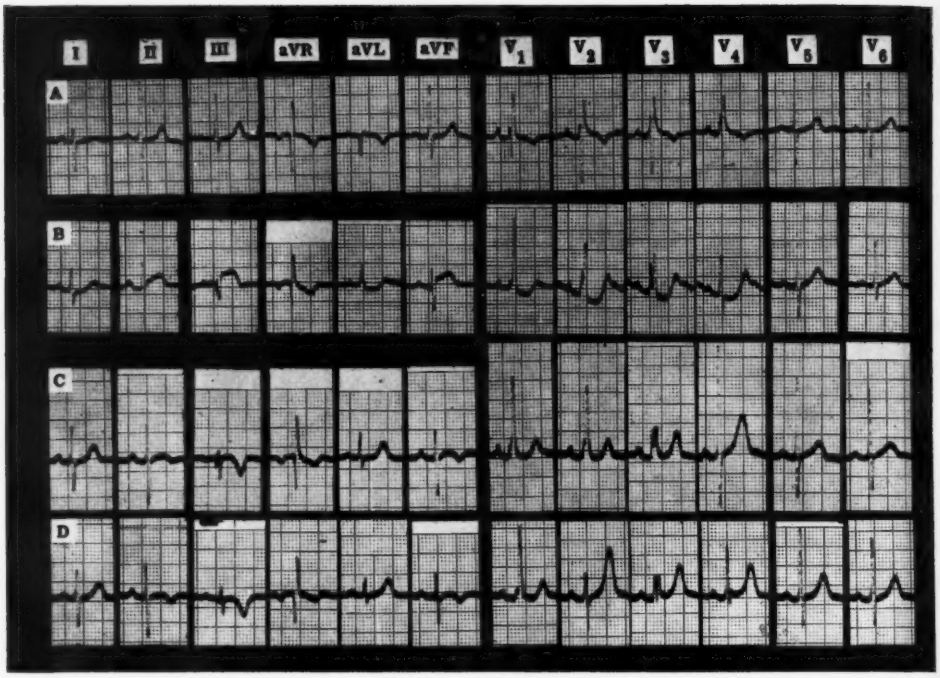


FIG. 3.—Serial electrocardiograms, (A) eight days before aortography; (B) on the day following aortography; (C) nine days after aortography; (D) three weeks after aortography.

DISCUSSION

It is paradoxical that the inclusion of pressure records during this procedure should have obscured the fact, obvious in retrospect, that the right coronary artery had been catheterized. Clearly, an awareness that such pressure wave forms may be recorded from the coronary artery is of the first importance practically and would, in this instance, have prevented the major insult to the myocardium.

It is of interest to consider how such pressure waves may be found in this situation. It is recognized that catheterization of the coronary sinus in man may yield wave forms of magnitude and shape closely, if not exactly, resembling ventricular forms (Culbertson *et al.*, 1949; Gregg, 1950; Miller *et al.*, 1953; Harris and Summerhayes, 1955).

Gregg (1950) has shown that a fall in central coronary artery pressure results in increased peripheral resistance in the coronary circulation. It may be that the catheter, at one stage in its advance down the coronary artery, occluded it only during systole, the mean pressure beyond this point falling and coronary arteriolar constriction occurring. The situation may then have resembled experimental conditions that have been described for the study of intramyocardial pressures.

Johnson and DiPalma (1939) imbedded isolated sections of carotid artery at varying depths in the left ventricular myocardium and showed that pressure changes within these segments were of ventricular form. Gregg and Eckstein (1941) showed that these pressures were subject to gross artefacts from distorsions and movements of the section, and attempted to avoid such artefacts by protecting the section from such influences with a fenestrated tube. They found that pressures within such protected sections approximated closely to the left ventricular pressures, despite the

important, variable, and unknown quantity of local muscle stretch due to the presence of the section within it. Because of this unknown factor they concluded that the method, while useful to give directional changes of pressure during the cardiac cycle, was not suitable for measuring those changes. Nevertheless, pressure waves closely approximating the ventricular pressures in magnitude and form were demonstrated. Gregg (1950) has also shown that, following experimental occlusion of a coronary artery in the dog, the pressure waves in the same vessel distal to the block, following development of collateral circulation, may be of central coronary or aortic type if the collaterals are predominantly superficial, but of ventricular form if the collaterals are deeply buried in the myocardium.

Further work by Johnson (1945), who used a similar method in attempts to measure intramyocardial pressure, indicated that one of the factors influencing this was the resistance to muscle shortening. His findings suggested that, with increasing aortic resistance, contractions of the left ventricle become more nearly isometric, and intramuscular pressure approaches a measure of the full force of contraction. In the case here recorded it may be relevant that the catheter was in the wall of the right ventricle and that there was severe pulmonary stenosis.

The finding of atrial pressure when the catheter was completely "wedged" suggests that the resulting complete cessation of coronary flow may cause arteriolar relaxation, possibly as the result of local anoxia and metabolite accumulation (Gregg, 1950), so that right atrial pressures are transmitted to the catheter in a manner analogous to the obtaining of pulmonary "wedge" pressures. We have subsequently catheterized the right coronary artery in the dog and have found atrial pressures when the catheter was completely wedged.

The significance of the systemic hypertension that developed during the procedure is uncertain.

Summary

The dangers of coronary artery catheterization and of repeated injections of radio-opaque material, which will enter the coronary tree in some concentration, are reiterated.

A case is reported in which pressure records from the right coronary artery, inadvertently catheterized, were misinterpreted as indicating the presence of the catheter in ventricle and atrium in turn.

The mechanisms by which such pressures may be developed in the coronary artery are discussed, and the practical importance of recognizing that such pressure wave forms may be found with the catheter so dangerously malpositioned is stressed.

The propriety of searching for the aortic valve orifice, or of any other exploration by retrograde aortic catheter in the region of the valve, is questioned in the light of this case.

We are grateful to Dr. P. R. Evans for permission to publish details of his case and to Dr. Charles Baker for encouragement and advice in the preparation of this report.

References

Brodén, B., Jönsson, G., and Karnell, J. (1949). *Acta Radiol.*, **32**, 498.
Culbertson, J. W., Halperin, M. H., and Wilkins, R. W. (1949). *Amer. Heart J.*, **37**, 942.
DiGuglielmo, L., and Guttadauro, M. (1952). *Acta Radiol.*, Supp. 97.
Gregg, D. E. (1950). *Coronary Circulation in Health and Disease.* Henry Kimpton, London.
——, and Eckstein, R. W. (1941). *Amer. J. Physiol.*, **132**, 781.
Harris, P., and Summerhayes, J. L. V. (1955). *Brit. Heart J.*, **17**, 453.
Helmsworth, J. A., McGuire, J., and Felson, B. (1950). *Amer. J. Roentgenol.*, **64**, 196.
Johnson, J. B., Lawlah, J. W., McFadden, F., and Dyer, J. F., Jr. (1957). *Amer. Heart J.*, **53**, 40.
Johnson, J. R. (1945). *Fed. Proc.*, **4**, 37.
——, and DiPalma, J. R. (1939). *Amer. J. Physiol.*, **125**, 234.
Jönsson, G., Brodén, B., and Karnell, J. (1951). *Acta Radiol.*, Supp. 89.
Miller, G. Kaplan, B. M., and Katz, L. N. (1953). *Amer. Heart J.*, **46**, 857.
Pearl, F., Friedman, M., Gray, N., and Friedman, B. (1950). *Circulation*, **1**, 1188.
Thal, A. P., Lester, R. G., Richards, S. R., and Murray, M. J. (1957). *Surg., Gynec., Obstet.*, **105**, 457.
Zimmerman, H. A., and Hellerstein, H. K. (1951). *Circulation*, **3**, 95.
——, Scott, R. W., and Becker, N. O. (1950). *Circulation*, **1**, 357.

THE ELECTROCARDIOGRAM IN PROGRESSIVE MUSCULAR DYSTROPHY

BY

G. W. MANNING AND G. J. CROPP*

From the Cardiovascular Unit, Department of Medicine, University of Western Ontario, Victoria Hospital, London, Ontario, Canada

Received February 28, 1958

From a survey of recent reports it is increasingly apparent that myocardial involvement is a fairly frequent sequel in progressive muscular dystropy. It has been estimated that the heart is affected in from 50 to 85 per cent of cases of progressive muscular dystrophy, and more commonly when this is of the childhood type (Berenbaum and Horowitz, 1956). Recent figures, provided by the Muscular Dystrophy Society of the United States have revealed well over 200,000 cases, and since cardiovascular complications are very likely, the problem would appear to be important, particularly in the differential diagnosis of obscure forms of heart disease, now grouped under the term isolated or idiopathic myocarditis. Nothacker and Netsky (1950) reported lesions in the cardiac muscle identical with lesions found in the skeletal muscles. Others (Bevans, 1945; Weisenfeld and Messinger, 1952; Rubin and Buchberg, 1952) have described similar cardiac involvement by the dystrophic process. Histological examination revealed an increase in connective tissue with atrophic muscle cells and fatty replacement, especially in the right ventricle. No descriptions of significant coronary artery disease have appeared. Although pathological studies have shown that the disease is not related to disturbances of blood supply and that the myocardial lesions are very similar to those seen in the skeletal muscle, they have provided little or no information with regard to the ætiology of the dystrophic process.

The clinical manifestations of heart disease in progressive muscular dystrophy are non-specific according to Rubin and Buchberg (1952). These authors and others (Weisenfeld and Messinger, 1952; Berenbaum and Horowitz, 1956) have described tachycardia, cardiac arrhythmias, cardiac enlargement in the absence of the usual causes, congestive failure, and electrocardiographic abnormalities of no specific pattern. Among a number of reports about the cardiographic changes, Weisenfeld and Messinger (1952), in a study of 44 cases, reported that tachycardia, abnormalities of the P wave, and tall R waves in V1 and V2 were of frequent occurrence, and this is the nearest approach to the description of any specific pattern. Rubin and Buchberg (1952) confirmed the high percentage of cardiac involvement in progressive muscular dystrophy, and found that very few of these patients had any clinical evidence of heart disease, although, some did present with congestive failure and others with disturbing arrhythmias and tachycardia: abnormal Q waves and a short P–R interval were the features emphasized in their review of 33 cases. A variety of electrocardiographic abnormalities has been described and these are much more frequent than the clinical manifestations of cardiac involvement, and are likely to precede, often by a considerable time, the appearance of clinical heart disease. This study of 38 cases pays particular regard to the incidence and characteristic features of these abnormalities in progressive muscular dystrophy.

Materials. Through the co-operation and assistance of the Muscular Dystrophy Association of London, Ontario, 38 cases of progressive muscular dystrophy have been studied, 28 in the juvenile group and 10 in the adult or facio-scapulo-humeral group. All had been carefully reviewed by

* This work was supported by the Ontario Heart Foundation and the Defence Research Board of Canada.

the neurological consultants and accepted as progressive muscular dystrophy of the pseudo-hypertrophic or facio-scapulo-humeral types. The two groups are considered separately because of the very obvious differences found in the electrocardiogram of the juvenile as compared to the adult type. Furthermore, such a division appears reasonable when one considers the neurological manifestations of the disease. The juvenile or pseudo-hypertrophic groups show a less localized and more widespread type of involvement and are, therefore, more likely to include the myocardium than the more localized facio-scapulo-humeral groups, which present as a clinical problem later in life.

Results

Pseudo-hypertrophic Muscular Dystrophy. In this group there were 28 cases. At the time of this study, the average age was 16, with a range of 5–37 years. The average age for onset of symptoms was 6 years with a range of 0–14 years. Twenty-two cases were confined to a wheeled chair or very limited walking and six were ambulatory. Chest deformities were not very common, nor of advanced degree, but were present in 9 cases—6 with funnel chest and 3 with scoliosis. Five of the 28 revealed clinical evidence of heart disease or cardiac involvement: in two of them the findings were very suggestive of associated congenital heart disease, and the remaining three gave a history of dyspnœa, and one of these had congestive failure (Fig. 1). Systolic murmurs were present in eight cases. Blood pressure was found to be within the normal range with one exception where it was 154/100. The heart rate was from 65 to 135 and contrary to previous reports tachycardia was not a feature in this series, though five were slightly above the upper limits of normal for their age.

Although there were a number of T wave abnormalities of a non-specific type, from flat to negative in the limb and lateral præcordial leads, the most prominent abnormality was found in the R wave amplitude in lead V1 and in the presence of abnormally deep Q waves in the limb and lateral chest leads (Fig. 2). Contrary to previously reported studies we found no significant variation from the normal in the P waves, P–R interval, cardiac rhythms, QRS, or Q–T duration. Since one expects large R waves in the younger age groups a very careful study of the Q and R V1 wave amplitudes was carried out in accordance with the standards described by a number of authors (Lepeschkin, E., 1951; Ziegler, 1951; Amer. H. Assoc., 1956; Nadas, 1957) (Fig. 3).

In these twenty-eight cases the following electrocardiographic features were noted.

The rate and rhythm were unchanged in most patients, but one had nodal rhythm, four ventricular extrasystoles, and one a shifting pacemaker.

The P wave amplitude was high in six cases and low in one; the remainder were normal.

The P–R interval and QRS duration were within normal limits in all of these cases.

Axis deviation occurred in eight cases, being left in four and right in four.

In 20 of the 28 cases, abnormally deep Q waves were present in the limb and/or lateral chest leads, V4, V5, and V6.

All had tall R waves in lead V1, 20 showing abnormally tall R waves, with an additional three at the upper limit of normal, in this lead (Fig. 3).

The R wave duration in lead V1 ranged from 0·02 to 0·08 sec., being 0·02 in one, 0·03 in eleven, 0·04 in ten, 0·05 in one, 0·06 in three, and 0·08 in two cases.

An RSR′ pattern in lead V1 was observed in four cases.

Low voltage was observed in three cases in the limb leads.

Most cases showed no variation in the S–T segment but this was depressed in lead V2 in one and elevated in V2 in one. S–T depression was noted in leads III and aVF in one other case.

T wave abnormalities ranging from flat to negative waves were noted in the limb and/or lateral V chest leads in 13 cases. A Q1T1 pattern occurred in two and a QIIITIII pattern in two.

In 25 cases U waves were present, of which all were positive and 9 very prominent.

To sum up the electrocardiographic findings. Twenty-five of the 28 were considered to be abnormal, two questionable (possibly normal), and only one completely normal in all respects.

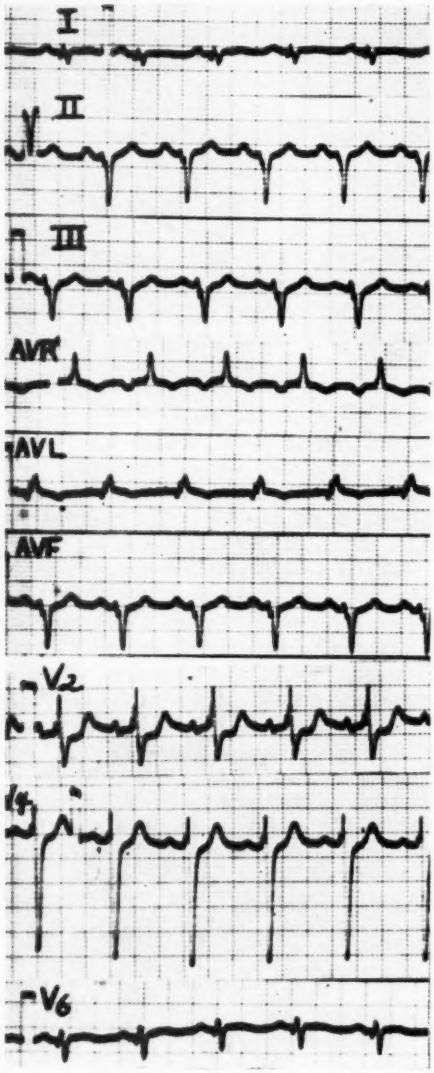


FIG. 1.—Man, aged 29, with classical pseudo-hypertrophic muscular dystrophy. Admitted with congestive failure, with cardiac enlargement, a mid-diastolic gallop rhythm, but no cardiac murmurs.

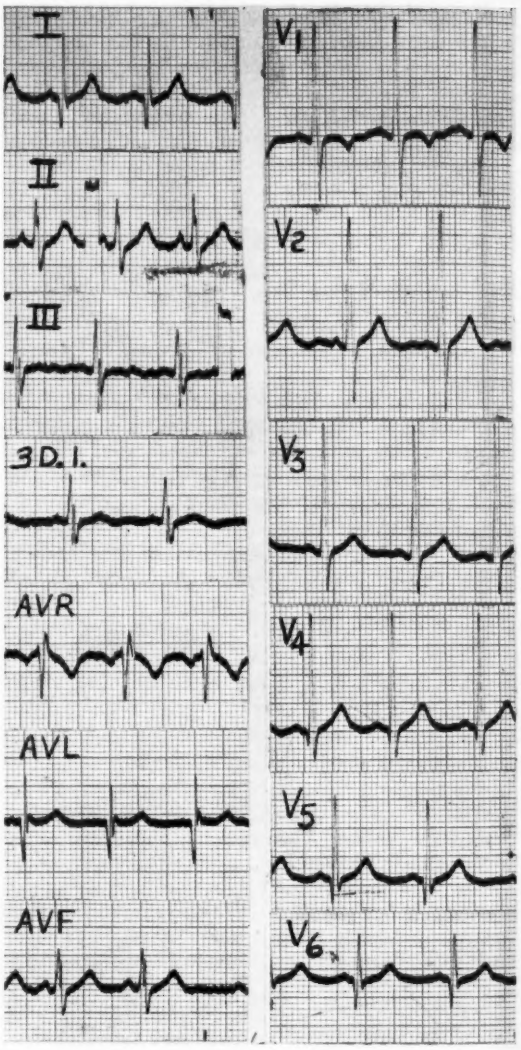


FIG. 2.—Boy, aged 13, with classical pseudo-hypertrophic muscular dystrophy. No clinical cardiac manifestations. Note deep Q waves in leads I and V6 and tall R in lead V1, typical of this series.

The major and most consistent finding was the presence of abnormally deep Q waves and abnormally tall R waves in lead V1.

Facio-scapulo-humeral Group. In the ten cases the average age at the time of this study was 44 years (range 14–67 years). The average age of onset of symptoms was 16 years. Five patients were

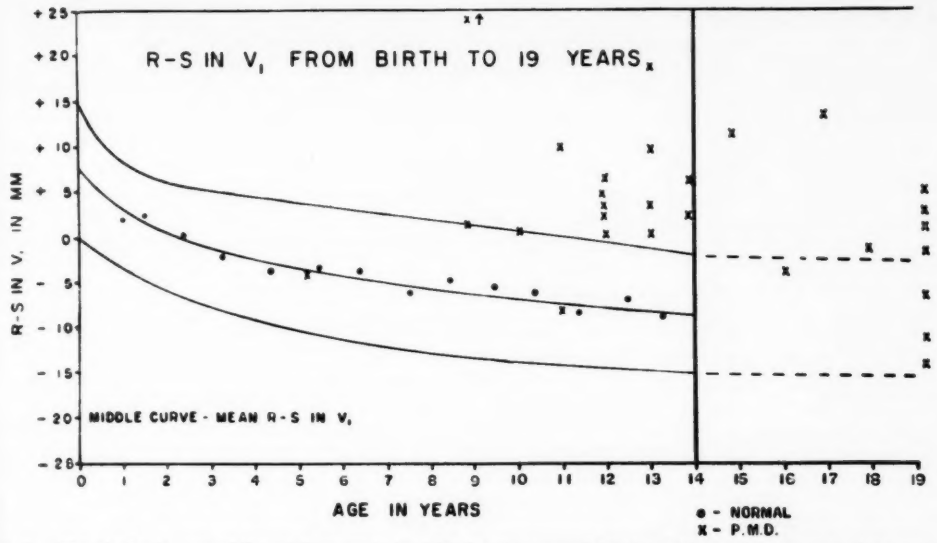


FIG. 3.—The algebraic sum of R and S waves in lead V1 for the normal (Nadas, 1957) and for twenty-eight cases of pseudo-hypertrophic muscular dystrophy from this study.

ambulatory and five confined to bed or wheel chair. There were five examples of left axis deviation in the electrocardiograms of this group. There were, however, only two cases with significant cardiographic abnormalities. One had rheumatic heart disease with mitral stenosis and auricular fibrillation, and the other, a man aged 67, showed classical left bundle-branch block, and second degree A-V block which was quite likely due to coronary sclerotic heart disease. The high incidence of large R in V1 and deep Q waves noted in the juvenile group was not apparent. There was only one case in which the R in V1 approached the upper limit of normal, and this occurred in a boy aged 14, the youngest patient of the group. One woman, aged 67, presented deep Q waves in lead III and AVF, together with well-marked left axis deviation.

DISCUSSION

From previous studies it is apparent that muscular dystrophy may involve the myocardium as well as the skeletal muscle. The two most commonly recognized types of progressive muscular dystrophy are the pseudo-hypertrophic form of childhood and the facio-scapulo-humeral type with onset at puberty. According to published reports the incidence of cardiac manifestations varies considerably, electrocardiographic changes being the earliest and most common manifestation. Walton and Nattrass (1954) in an excellent review of the myopathies reported normal findings in 36 out of 48 cases of the Duchenne type of muscular dystrophy, but only the standard limb leads and lead CF4 were recorded. In our study over 70 per cent of the juvenile pseudo-hypertrophic group revealed abnormal electrocardiographic patterns of a specific nature as compared with the facio-scapulo-humeral group who showed no such patterns and, in fact, little or nothing abnormal. In our series of cases the most interesting and significant findings were confined to the Q waves, and the R wave amplitude in lead V1 (Fig. 2).

From this study it is apparent that the earliest cardiac manifestations in the pseudo-hypertrophic cases occur in the electrocardiogram (Fig. 2 and 3). Furthermore, no such changes were noted in the facio-scapulo-humeral group. In view of the current clinical and pathological concept of these two groups of progressive muscular dystrophy it seems reasonable to expect myocardial

changes more frequently and earlier in the pseudo-hypertrophic juvenile group. The findings in this study are in keeping with this view, indicating more widespread disease involving the myocardium in the juvenile group. Furthermore, in view of the high incidence of abnormally tall R waves in lead V1 (and deep Q waves) it would appear that the electrocardiograph should be of value in the diagnosis of muscular dystrophy and also in differentiating the two groups.

Although no pathological studies have been carried out on these cases there appears to be no reason to suspect right ventricular hypertrophy as the mechanism producing tall R waves in lead V1. A more reasonable explanation would appear to be associated with myocardial damage disturbing the initial QRS vector. The major abnormality appears to be a persistence of an infantile vector loop pattern which in the age groups studied is abnormal by all the accepted standards (Fig. 3).

Summary

Abnormally deep Q waves and tall R waves in lead V1 were present as a specific feature in 70–75 per cent of the electrocardiograms in 28 cases of pseudo-hypertrophic muscular dystrophy.

In ten cases of facio-scapulo-humeral muscular dystrophy the Q and R V1 patterns were normal.

Clinical manifestations of cardiac disease were rare in this study.

The specific electrocardiographic abnormality in pseudo-hypertrophic muscular dystrophy appears to be the persistence of an infantile QRS pattern.

Sincere appreciation and thanks are expressed to the Muscular Dystrophy Association, London, Ontario, for their co-operation and assistance in providing patients for this study.

We are indebted to W. B. Saunders, Philadelphia, for Fig. 3, which is a modification of a diagram illustrating the normal R and S amplitudes from Nadas (1957).

References

American Heart Association (1956). *Electrocardiographic Test Book*. Vol. 1. American Heart Association Incorporated, New York.

Berenbaum, A. A., and Horowitz, W. (1956). *Amer. Heart J.*, **622**, 51.

Bevans, M. (1945). *Arch. Path.*, **40**, 225.

Lepeschkin, E. (1951). *Modern Electrocardiography*. Williams & Wilkins Company, Baltimore, p. 138.

Nadas, A. S. (1957). *Pediatric Cardiology*. W. B. Saunders, Philadelphia, p. 69.

Nothacker, W. G., and Netsky, M. G. (1950). *Arch. Pathol.*, **50**, 578.

Rubin, I. L., and Buchberg, A. S. (1952). *Amer. Heart J.*, **43**, 161.

Walton, J. N., and Nattrass, F. J. (1954). *Brain*, **77**, 169.

Weisenfeld, S., and Messinger, W. J. (1952). *Amer. Heart J.*, **43**, 170.

Ziegler, R. F. (1951). *Electrocardiographic Studies in Normal Infants and Children*. Charles C. Thomas, Springfield.

CASE REPORTS

PATENT DUCTUS ARTERIOSUS WITH VENTRICULAR SEPTAL DEFECT

BY

G. L. HIGGINS

From the Southmead Hospital, Bristol

The case described below is of interest in that the patient survived until the age of 69 with a double congenital lesion, complicated by essential hypertension.

Case Report

A woman, aged 58, was admitted to Snowdon Road Hospital, Bristol, in 1945, with a twenty-year history of dyspnœa, palpitation, occasional ankle swelling, and various neurotic symptoms. On examination, she was found to have kyphoscoliosis and emphysema. The pulse was regular; the apex beat was in the left sixth intercostal space beyond the midclavicular line. The heart sounds were normal, with a basal and central systolic murmur and thrill, and the blood pressure was 190/100 mm. Hg. The electrocardiogram then and again ten years later was normal. Chest X-ray showed cardiac enlargement of unspecified degree. These findings were noted by three consultant physicians who had examined her on various occasions about this period.

She remained, with the exception of a few months, in this hospital for the chronic sick until her death in 1956. Re-examined in 1955, she was found to be apprehensive, with symptoms of dyspnœa, orthopnœa, paroxysmal nocturnal dyspnœa, and dependent œdema. There was no cyanosis or finger clubbing. The venous pressure was raised, the jugular veins being distended to 2·5 cm. above the clavicles in the sitting position. The pulse rate was 100 a minute, regular, and collapsing in character. The blood pressure had risen to 260/140 mm. The apex beat was in the left sixth intercostal space at the anterior axillary line, heaving in character. The heart sounds were tic-tac; the pulmonary second sound was split. There was a loud machinery murmur in the pulmonary area, and also a separate systolic murmur with a thrill at the sternal border in the left fourth intercostal space.

The clinical diagnosis was patent ductus arteriosus with a ventricular septal defect, complicated by systemic hypertension and congestive heart failure. Her condition gradually deteriorated, and she died suddenly at the age of 69, in 1956, nearly 11 years after her admission.

Necropsy. The heart weighed 381 g. There was left ventricular hypertrophy (average thickness 12·5 mm.); the right ventricle was also hypertrophied (thickness 6 mm.); both chambers were dilated. The mitral, tricuspid, and pulmonary valves were normal; there was some adherence of the aortic cusps. Below the pulmonary valve, in the muscular part of the septum, near the fibromuscular junction, there was a defect, 18 mm. in diameter, in its right ventricular face, passing obliquely through the septum, so that it was 4 mm. at its left ventricular face. The aorta was not dilated, the circumference immediately above the valve being 67 mm. (normal=50–90 mm.); in addition there were severe atheromatous changes throughout its length, these being greatest in the abdominal aorta. The pulmonary artery, immediately above the pulmonary valve, was 48 mm. in circumference, with many intimal atheromatous patches; the smaller pulmonary arteries and arterioles showed no evidence of pulmonary hypertension. There was a patent ductus arteriosus, 17 mm. in length, running obliquely through adhesions between the aorta and left pulmonary artery. The aortic orifice, situated in a small localized dilatation, was 8×5 mm. in size. Around the pulmonary orifice, which was 2 mm. in diameter, was a spout-like elevation of the intima, about 1 mm. high. The kidneys showed changes of essential hypertension. The lungs showed bronchopneumonic changes.

Discussion

The two main features of interest in this patient are the age to which she survived and the apparent change in physical signs. The life span in patients with patent ductus arteriosus may be

normal and the following examples have been recorded, together with data of the ductus size. The size of the ductus and the size of the pressure gradient between the aorta and the pulmonary artery are the two factors that determine the size of the shunt, and hence the prognosis of the patient. It would seem that the smaller the ductus the better the prognosis as to life span.

Author	Patient's sex and age at death	Aperture of ductus	
		Aortic	Pulmonary
Josefson (1897)	F. 66	6×10 mm.	4 mm.
White (1928)	F. 65	10 mm.	4 mm.
Brody and Randall (1935)	F. 66	9 mm.	4 mm.
Walker and Ellis (1940)	M. 73	—	—
Fishman and Silverthorne (1951)	F. 75	3 mm.	4 mm.
Higgins (1958)	F. 69	8×5 mm.	2 mm.

In addition, in this patient there were two additional factors in that she had hypertension and a ventricular septal defect—factors that might reasonably be presumed to have shortened the life span. It is fair to point out that the patient had been sheltered in hospital for at least ten years, and that for the greater part of her life she had been an invalid, not so much as a result of her cardiac condition, but as a result of a chronic neurosis with feelings of insecurity dating from childhood.

The apparent change, if we accept it, of a basal systolic murmur to a machinery murmur also requires comment. The presence of right ventircular hypertrophy and pulmonary artery atheroma

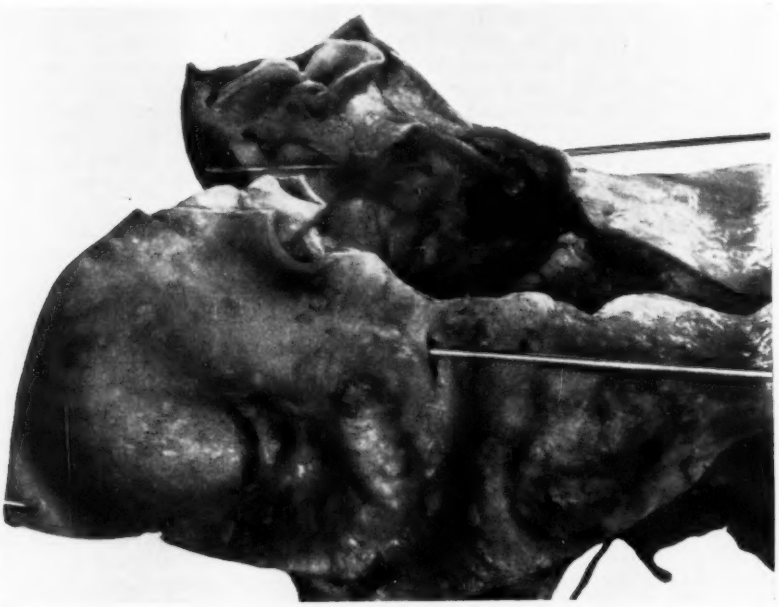


FIG. 1.—The aorta is seen in the foreground with the probe entering the aortic orifice of the ductus. Below and to the left are the openings of the innominate, left common carotid, and left subclavian arteries. The back of the specimen has been shown by arranging a mirror so that it is reflected, somewhat above the front view, and the same probe is seen leaving the pulmonary orifice of the ductus.

may be due not only to the shunts but also to pulmonary hypertension, although there were no changes in the pulmonary arterioles suggestive of this. If so, the pressure gradient between the aorta and pulmonary artery would be relatively low, and hence there might be a systolic murmur only. Later, when the systolic blood pressure was continuously in the region of 260/140 mm., the gradient became greater and led to the production of a continuous murmur. Alternatively, it seems possible that the continuous murmur was present but was not noted.

Summary

A woman with a persistent ductus arteriosus and a ventricular septal defect, who survived until the age of 69 although she had also essential hypertension, is described, together with autopsy findings.

Comments are made on the life span and the size of the ductus.

I am grateful to Dr. J. A. Cosh for his helpful criticism in preparing this case report, to Dr. J. M. Naish for permission to publish it, and to Dr. N. J. Brown for the post-mortem findings.

References

Brody, J. G., and Randall, A. (1935). *Ohio State med. J.*, **31**, 599.
Fishman, L., and Silverthorne, L. C. (1951). *Amer. Heart J.*, **41**, 762.
Josefson (1897). *Novd. med. Arkiv.*, **7**, 1.
Walker, G. C., and Ellis, L. B. (1940). *Proc. New Eng. Heart J.*, **41**, 26.
White, P. D. (1928). *J. Amer. med. Ass.*, **91**, 1107.

PATENT DUCTUS ARTERIOSUS WITH MITRAL STENOSIS

BY

J. MACKINNON AND R. M. BRIGGS

From the Departments of Cardiology and Thoracic Surgery, Manchester Royal Infirmary

An apical mid-diastolic murmur is sometimes audible in patients with a patent ductus arteriosus (Nadas and Alimurung, 1952) but differentiation from organic mitral stenosis is usually not difficult. The patient described in this paper presented with typical murmurs of isolated mitral stenosis and the correct diagnosis of patent ductus arteriosus and trivial mitral stenosis was made only at operation.

Case Report

The patient, a young woman of 19, gave no history of rheumatic fever or chorea. She was first seen by Professor Crighton Bramwell at the age of 6 in 1943. No record is available of the findings at that time except that a standard lead electrocardiogram showed left axis deviation. She was seen again by the same physician in 1949, when the classical physical signs of mitral stenosis were found and the fluoroscopic findings were described as those of an uncomplicated mitral lesion. His comment on the case was " Only the fact that the cardiac abnormality was noticed so early in life made me think there must be an associated congenital lesion."

Between 1949 and 1956 the patient was examined on separate occasions by six different observers all of whom considered she had the classical signs of mitral stenosis. These physical signs were as follows.

There was no cyanosis and normal sinus rhythm. The blood pressure was 110/70–120/80. The cardiac impulse was diffuse and palpable almost out to the anterior axillary line. An apical diastolic and presystolic thrill was palpable. On auscultation the mitral first heart sound was loud and there was an opening snap. The pulmonary second sound was loud and split. A loud, full mitral diastolic murmur with presystolic accentuation was present and there was a soft apical systolic murmur. On one occasion only, a soft diminuendo diastolic murmur was heard at the lower end of the sternum. The lungs were always clear and there were no signs of congestive heart failure.

Fluoroscopy on several occasions showed the heart to be moderately enlarged and of mitral configuration. Moderate left atrial enlargement was demonstrated and the lung fields showed increased vascularity but no hilar dance.

The electrocardiogram showed slight depression of the S–T segment in aVL and in lead I and although a large R wave was present in V3R there was no other evidence of right ventricular enlargement. Some delay (0·06 sec.) in the onset of the intrinsic deflection, suggesting left ventricular enlargement, was present in V4 and V6 but this was not noted until the record was re-examined after operation.

Towards the end of 1955 the patient began to notice increasing breathlessness on exertion but had no paroxysmal dyspnœa or hæmoptysis. Her incapacity steadily increased until April, 1956, when mitral valvotomy was advised.

At thoracotomy Mr. W. F. Nicholson noted considerable left ventricular enlargement and a grossly dilated pulmonary artery over which a continuous thrill was palpable. The pulmonary veins were large and there was moderate left atrial enlargement. Palpation of the mitral valve revealed a lightly calcified valve, only slightly stenosed and approximately 3 cm. in diameter. The lateral commissure split easily to give a valve of 3·5 cm. No attempt was made to split the medial commissure. Thorough palpation of the left atrium revealed no atrial septal defect; but after further dissection a broad patent ductus arteriosus was isolated and ligated with cessation of the thrill over the pulmonary artery. Seven hours after operation she collapsed due to bleeding which ceased when the ductus was divided and sutured.

All murmurs disappeared immediately after operation and the heart sounds became normal. Six months after operation her exercise tolerance, heart size, and pulmonary vascularity were within normal limits (Fig. 1B).

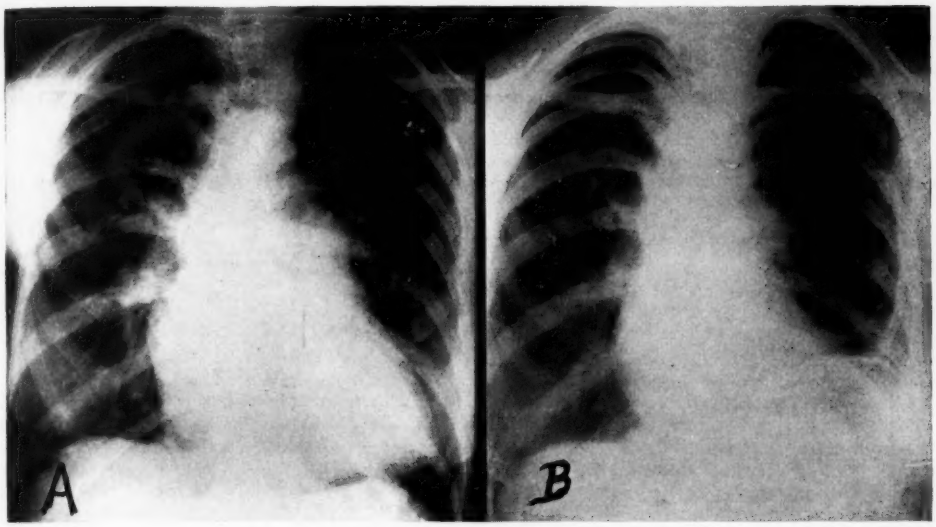


FIG. 1.—Teleradiograms of patient. (A) Showing cardiac enlargement and increased pulmonary vascular markings extending well out into the lung fields. (B) After ligation of the ductus, showing diminution of heart size and return of pulmonary vascularity to normal. Elevation of the left hemidiaphragm is due to damage to the phrenic nerve at the second operation.

Discussion

Bramwell (1943) pointed out that the production of an obstructive murmur depends on the degree of obstruction relative to the velocity of the blood current: he suggested that an increased rate of blood flow through a normal mitral orifice may be instrumental in producing accentuation and roughening of the first heart sound in thyrotoxicosis and in other conditions in which the heart is over-acting. Patent ductus arteriosus is associated with a large pulmonary flow and an increased flow through the mitral valve, and the apical mid-diastolic murmur not uncommonly heard in the uncomplicated patent ductus probably arises as a result of this (Nadas and Alimurung, 1952). These signs may be regarded as signifying a relative mitral stenosis (Bramwell, 1943) and disappear when the ductus is ligated. In our patient the mitral valve was slightly stenosed and it seems likely that a large increase in blood flow through this slightly narrowed valve caused the auscultatory findings of mitral stenosis.

We cannot explain the absence of the typical ductus murmur. In the presence of pulmonary hypertension the typical murmur may be modified or absent (Whitaker *et al.*, 1955) and the diagnosis difficult or impossible to make without the aid of cardiac catheterization or angiocardiography. Possibly our patient had some degree of pulmonary hypertension as a result of the increased pulmonary blood flow and the mitral lesion, but the evidence suggests that the shunt was predominantly left to right.

Although the ductus was silent three atypical features should have aroused our suspicion: the early age at which well-developed mitral stenosis was found, the signs of left ventricular enlargement in the cardiogram without mitral regurgitation, and the evidence on radioscopy of increased pulmonary blood flow.

The ætiology of the mitral lesion remains unknown. No previous history of rheumatism or chorea was obtained and sections of the atrial appendage removed at operation showed no evidence of rheumatic activity.

Summary

A case of patent ductus arteriosus with slight mitral stenosis presenting with signs simulating severe mitral stenosis has been described. The correct diagnosis was established only at operation. All physical signs disappeared after ligating the ductus and slightly increasing the size of the mitral valve by valvotomy.

Our thanks are due to Professor Crighton Bramwell for allowing us to quote his original report and to Dr. A. Morgan Jones, Mr. W. F. Nicholson, and Dr. E. G. Wade for help and advice in the preparation of this report, and for permission to publish the case.

References

Bramwell, C. (1943). *Brit. Heart J.*, **5**, 24.
Nadas, A. S., and Alimurung, M. M. (1952). *Amer. Heart J.*, **43**, 691.
Whitaker, W., Heath, D., and Brown, J. M. (1955). *Brit. Heart J.*, **17**, 121.

EDITORIAL NOTE

This case recalls a somewhat parallel example that occurred in the clinic of Professor Gustav Nylin in the Sodersjukhuset, Stockholm, some years ago. It was demonstrated to one of the editors (I.G.W.H.) in 1951, who was greatly impressed at the time by the fact that this error in diagnosis was exhibited and discussed in detail by so eminent a clinician. The case has not been published and we are enabled through the courtesy of Professor Nylin to give the following details.

The patient was a lady of 38 who came under observation in 1947 with a clinical diagnosis of mitral stenosis. There was a long diastolic murmur confirmed by phonocardiogram and she had a blood pressure of 145/98. There was an enormous bulging pulmonary artery on X-ray which was considered due to an atrial septal defect. In 1949 she was admitted after three weeks' illness with low fever, and was regarded as a case of subacute bacterial endocarditis. The apical diastolic murmur was noted to be of a rumbling character. Blood cultures were negative. Her temperature resolved with penicillin but she died suddenly shortly afterwards. The ante-mortem diagnosis was thrombosis or embolus of a pulmonary artery with Lutembacher's syndrome.

At necropsy there was, in fact, thrombosis of the left pulmonary artery and a congenital mitral stenosis. There was no atrial septal defect but a large persistent ductus arteriosus.

INCOMPLETE RUPTURE OF THE ASCENDING AORTA WITH SECONDARY ANEURYSM

BY

JOHN WEDGWOOD

From Addenbrooke's Hospital, Cambridge

Case reports of incomplete rupture of the aorta with aneurysm formation due to stretching of the weakened aortic wall, without dissection, are rare. The following case is of interest because of its rarity, its possible traumatic ætiology, and the patient's long survival.

Case Report

A previously healthy farm worker, aged 27 years, was admitted to Addenbrooke's Hospital, as an emergency, under Dr. Leslie Cole, on March 16, 1949. He complained of severe pain in the chest.

The evening before admission, he had been walking home from a football match, where he had been an enthusiastic spectator, when he was suddenly struck by a severe pain in the back and chest. The onset was " as if an arrow had hit him between the shoulder blades." The pain was felt all over the chest. It was maximal under the sternum and radiated into the neck, back, epigastrium and later the right shoulder. The pain soon became agonizing; it was " tearing " in character and made worse by breathing. He felt very ill and sweated profusely. He managed to walk to his house about 40 yards away. The pain lasted all night, preventing sleep, and was associated with retching and vomiting. He was admitted to his local hospital and later transferred with a provisional diagnosis of ruptured œsophagus.

He had been a fit and active man before this illness. He worked as a farm labourer and was also a smallholder. He played football regularly at weekends. Three weeks before admission he had been thrown from his motor cycle and had fractured his left radius. There was no known chest injury or chest pain at the time. There was no past history of rheumatic fever and no other relevant past history.

The family history, most of which was supplied by the patient's general practitioner, Dr. J. K. Paterson, is of interest, although unfortunately incomplete. The patient's father died of carcinoma of the lung, aged 59; he was a stocky well-built man like the rest of his family. The patient's mother was apparently well; she had five sisters and two brothers; all with one exception were tall and thin. One of the brothers, killed in the 1918 war, aged 20, had been exceptionally tall, and was noted for his long delicate fingers. The patient had one brother, aged 34, who was said to have a bad heart.

On admission, about 24 hours after the onset, he was feeling better and had only a dull, aching pain in the centre of the chest and in the right shoulder tip, made worse by deep inspiration.

He appeared a healthy, muscular man about 6 ft. tall. He was afebrile although he ran a low-grade fever during the three days after admission. There was no evidence of arachnodactyly. His left forearm was in plaster. No abnormality was detected in the peripheral pulses and the femoral pulses were present and equal.

The most prominent physical sign was a loud aortic diastolic murmur heard best at the left sternal edge. The pulse was regular and not collapsing. The blood pressure on admission was raised (170/135) but later readings were lower and equal in both arms (140/70). There were no

signs of heart failure. There was no sternal pulsation or evidence of superior vena caval obstruction. There were signs of a raised diaphragm at the right lung base. There was some guarding and tenderness to palpation in the epigastrium. No other relevant abnormality was found. The urine contained no albumen or other abnormality on routine tests.

Chest X-ray and cardioscopy were performed by Dr. Brian Donnelly before the patient was taken to the ward. The superior mediastinum showed generalized broadening and its structures were completely obscured. The aortic arch was completely obscured together with the aortic window and aortic triangle in the left oblique position. The left ventricle was enlarged. The right diaphragm was raised and its movements limited. A barium swallow showed a normal œsophagus.

An electrocardiogram showed patterns of acute pericarditis (Fig. 1).

A full blood count showed: leucocytes, 12,400 per c.mm. with 76 per cent neutrophils (9424 per c.mm.); hæmoglobin: 16·3 g. per 100 ml. The blood W.R. and Kahn were negative.

A provisional diagnosis of dissecting aneurysm of the ascending aorta and aortic regurgitation was made. The patient was treated with strict bed rest and sedation. The day after admission he had no pain and felt reasonably well.

Three weeks later he had a further attack of chest pain lasting four hours and associated with fever of 100° F. Clinical examination showed the presence of a loud pericardial friction rub. The electrocardiogram again showed evidence of acute pericarditis (Fig. 1).

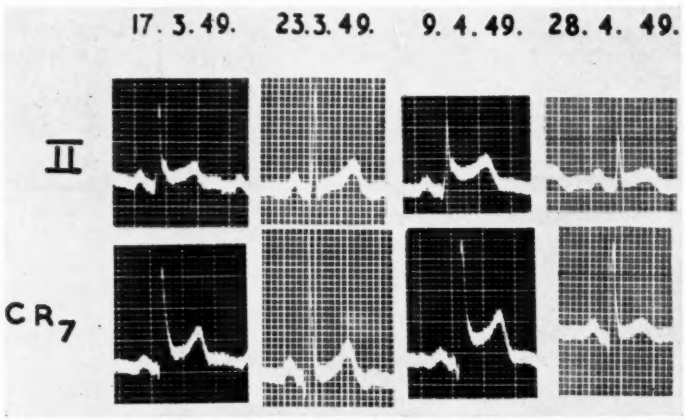


FIG. 1.—Serial cardiograms, showing recurrent patterns of acute pericarditis.

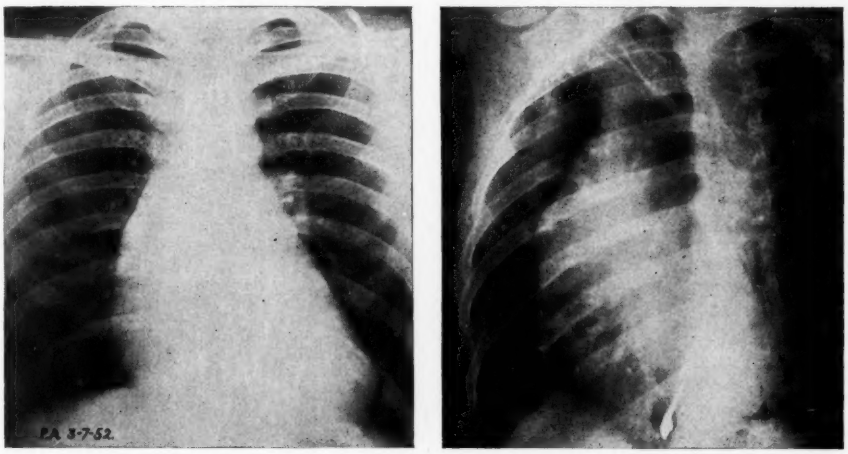
A third, but less severe attack of pain, also with evidence of acute pericarditis, occurred three weeks later.

The subsequent progress in hospital was uneventful. He was gradually allowed up and discharged, twelve weeks after admission. Examination before discharge showed the presence of aortic regurgitation (B.P. 140/90). Cardioscopy showed the appearances of an aneurysm of the ascending aorta with enlargement of the left ventricle.

He started light clerical work six months later. During the next two years he kept fairly well except for occasional sharp pains in the right side of his neck and a short attack of paroxysmal auricular fibrillation for which he was again admitted to hospital in March, 1951.

In 1952, he decided against advice, to start heavier work. He began work on his smallholding and also got married. In April, he developed persistent auricular fibrillation. There followed a gradual deterioration in his condition. He became progressively more short of breath

and the signs of aortic regurgitation increased. In May he had a further attack of chest pain, lasting a few minutes, which radiated down his left arm and woke him from sleep. Chest X-ray in July showed increased enlargement of the left ventricle and an increase in prominence of the aneurysm of his ascending aorta (Fig. 2).



A B

FIG. 2.—Chest X-rays, showing aneurysm of ascending aorta. (A) Postero-anterior view. (B) Left oblique view.

On September 30, 1952, about three years after his first symptoms, he developed another attack of chest pain which lasted all night. He was admitted to hospital on the following day, when he was found to be in congestive heart failure with rapid auricular fibrillation. There was no improvement with routine treatment and he died following multiple pulmonary embolisms one week later.

Post-mortem Examination.

The following are extracts from the report by Dr. A. M. Barrett.

Cardiovascular System. A ragged laceration of the greater part of the thickness of the ascending aorta completely encircles the vessel just above the aortic valve. The two margins of the laceration have been separated by a distance of about 5 cm., and in this gap the aortic wall consists only of a thin layer of fibrous tissue, except that there are a few raised islands formed by detached fragments of the original aortic wall. The smoothness of the inner surface of the fibrous tissue in the gap, and the rounding off of the margins of the laceration prove that the laceration is old.

There is an intrapericardial aneurysmal dilatation of the damaged ascending aorta (Fig. 3): the dilatation involves the aortic ring (11 cm. circumference), is maximal at about the middle of the gap (22 cm. circumference), and finishes at the origin of the carotid arteries.

The descending thoracic and abdominal portions of the aorta are normal in size, appearance, and elasticity (descending thoracic aorta immediately beyond the left subclavian artery, 5·3 cm. circumference; abdominal aorta, 4·3 cm. circumference): in the abdominal aorta, however, there are buttons of atheroma.

The aneurysm contains post-mortem blood clot only, except that there is a plug of ante-mortem thrombus peeping through an apparently recent secondary laceration, having abrupt margins, situated just above the right commissure of the anterior cusp of the aortic valve; and another similar plug of ante-mortem thrombus peeping through a smaller vertical recent laceration in one of the islands of detached aortic wall on the posterior aspect of the aneurysm.

The aortic valve is congenitally bicuspid and has been rendered incompetent by dilatation of the ring, with separation (0·5 cm.) of the adjacent cusps on the left, and stretching of the cusps.

The mitral, tricuspid, and pulmonary valves are normal. Nowhere have the lacerations extended for any considerable distance within the aortic wall: the aneurysm is not a dissecting aneurysm. Only a thin layer of fibrous tissue, however, separates the blood in the lumen of the aorta from the pericardial cavity, and it is very probable that there have been leakages of blood into the pericardium; for the pericardial cavity has been obliterated by fibrous adhesions which are not very tough, and in some places are stained greenish-brown as if by altered blood.

FIG. 3.—Photograph of the heart at necropsy, showing aneurysm of the ascending aorta.

Both left and right ventricles are greatly hypertrophied, and the endocardial surface of the left side of the interventricular septum shows the thrush's breast mottling of fatty degeneration.

A plug of ante-mortem thrombus fills the left auricular appendage. The coronary arteries and their orifices are well developed and healthy, showing only a slight degree of atheroma.

Histology. A longitudinal section of the ascending aorta taken through the upper border of the tear shows that the media of the aorta has been torn completely across, and in the gap between the separated borders of the tear the wall consists of thickened adventitial fibrous tissue, with an inner newly formed layer of connective tissue, in which there is much mucoid material with some delicate elastic fibrils. There

is no evidence of dissection into the healthy part of the aortic wall. A section of the aorta at the level of the diaphragm shows a considerable amount of interfibrillary mucoid material—more than I should have expected in a healthy patient of this age—but there is no true medionecrosis.

The lungs show congestive changes and two recent hæmorrhagic infarcts. The liver, spleen, and kidneys show chronic passive venous congestion.

Discussion

There was no dissection of the wall of the aorta in this case. The aneurysm appeared to be due to an incomplete and partially healed rupture of the ascending aorta with subsequent stretching of the weakened aortic wall. Pathologically this can be considered a " secondary true aneurysm " (Kaufmann, 1929). Reports of this condition are much less common than those of dissecting aneurysm. Search of the necropsy records at this hospital, over a nine-year period (1946–1955) revealed no similar cases, whereas there were 58 other cases of aortic aneurysm including 26 cases of dissecting aneurysm and 5 cases of syphilitic aneurysm.

The post-mortem appearances of incomplete rupture of the aorta with secondary aneurysm were discussed by Asahi (1905). Cases with both clinical and post-mortem records have been described by Heller (1904), Gravier (1924), Laves (1925), Lundberg (1930), Eskelund (1941), and Wenger (1943). In the six cases described by these authors and in the present case the site of rupture and secondary aneurysm formation, the occurrence of aortic regurgitation and death in congestive heart failure, were common features. Chest pain was rare and noted in Heller's case only. An additional finding in the present case was the clinical and electrocardiographic evidence of acute pericarditis. This appeared to be due to slow leakage of blood into the pericardium. Similar changes have been described in dissecting aneurysm (Levinson *et al.*, 1950) but are uncommon. The pericardium which invests the ascending aorta may favour the development of secondary aneurysm in the cases described in all of which rupture occurred a short distance above the aortic valves.

Survival for three years with an incomplete rupture of the aorta of this severity is exceptional. It is hoped that it was related to the strict rest which was enforced from the beginning of the patient's illness. His rapid deterioration when he returned to heavy work, against advice, confirms the importance of restricting the activities of these patients. The importance of adequate rest emphasizes the necessity for early diagnosis.

Complete tears of the aorta following severe chest injuries are well known. Direct injury to the chest is, however, not a common cause of either dissecting aneurysm (Shennan, 1934) or incomplete rupture of the aorta. In the case described by Heller (1904) incomplete rupture of the aorta appeared closely related to sudden strain, when the patient, who had been carrying a heavy girder with three other men, was left to take the weight by himself. In the present case there was no definite chest injury but it is possible that the initial rupture of the aorta took place in the motor-cycle accident three weeks before the onset of symptoms. Rice and Wittstruck (1951) reported a case of delayed traumatic rupture of the aorta and dissecting aneurysm following a motor accident. The patient, a pregnant girl of 20, struck the upper part of her chest against the seat in front of her but received a few external bruises only. Rupture of the aorta was attributed to rapid deceleration. This possible cause of rupture of the aorta in motor accidents has also been discussed by Tannenbaum and Ferguson (1948).

A healthy aorta is able to withstand exceptional pressures (Oppenheim, 1918) but in the present case there is reason to suppose that the aortic media was abnormal and more liable to rupture as a result of injury. The family history is also suggestive that this case may have been a " forme fruste " of Marfan's syndrome (Reynolds, 1950).

Aneurysm of the ascending aorta with aortic regurgitation is a common finding in Marfan's syndrome and incomplete tears of the aorta may also be found (Moses, 1951). The findings in the present case were in some respects similar except that the aneurysm appeared to have been caused by the tears in the aorta. The possibility that some degree of aortic dilatation and aortic incompetence had preceded the condition cannot be excluded.

Summary

A case is described of incomplete rupture of the ascending aorta with secondary aneurysm formation in a man aged 27 years. The rupture was also associated with aortic regurgitation and acute pericarditis. Recurrent episodes suggesting further tears occurred and death took place three years later from congestive heart failure with auricular fibrillation.

The rupture may have been caused by trauma but there was also some evidence that the aorta was abnormal and that the case may have been a " forme fruste " of Marfan's syndrome.

The importance of early diagnosis and adequate rest in suspected cases of rupture of the aorta is emphasized.

I thank Dr. Leslie Cole for permission to publish this case and Dr. A. M. Barrett for permission to publish the necropsy report and for help in the preparation of this paper. I would also like to acknowledge my thanks to the late Dr. Brian Donnelly for the X-rays and radiological findings. I am grateful to Dr. J. K. Paterson for the information about the patient's family history.

References

Asahi, K. (1905). *Z. Heilk.*, **26** (N.F. 6), 163.
Eskelund, V. (1941). *Ugeskr. Læg.*, **103**, 240.
Gravier, L. (1924). *J. Méd. Lyon*, **5**, 563.
Heller, A. (1904). *Dtsch. Arch. klin. Med.*, **79**, 306.
Kaufmann, E. (1929). *Pathology*. (Trans. Reimann), London, p. 147.
Laves, W. (1925). *Wien. klin. Wschr.*, **38**, 804.
Levinson, D. C., Edmeades, D. T., and Griffith, G. C. (1950). *Circulation*, **1**, 360.
Lundberg, A. (1930). *Acta med. scand.*, **73**, 19.
Moses, M. F. (1951). *Brit. med. J.*, **2**, 81.
Oppenheim, F. (1918). *Münch. med. Wschr.*, **45**, 1234.
Reynolds, G. (1950). *Guy's Hosp. Rep.*, **99**, 178.
Rice, W. G., and Wittstruck, K. P. (1951). *J. Amer. med. Ass.*, **147**, 915.
Shennan, T. (1934). *Dissecting Aneurysms*. M.R.C. Special Report Series, No. 193. H.M.S.O. London.
Tannenbaum, I., and Ferguson, J. A. (1948). *Arch. Path.*, **45**, 503.
Wenger, F. (1943). *Arch. Path.*, **36**, 253.

INCOMPETENT CONGENITAL BICUSPID RIGHT ATRIO-VENTRICULAR VALVE

BY

N. COULSHED

From the Regional Cardiac Centre, Sefton General Hospital, Liverpool

Congenital right atrio-ventricular incompetence is uncommon, but when present usually shows characteristic physical signs. The case to be presented was regarded during the last year of his life as having Ebstein's anomaly, the correct diagnosis being established at necropsy.

Case Report

A man, aged 18, was first seen at the Cardiac Centre in 1954, when he was admitted because of fainting attacks during the previous three months. In 1948, when aged 12, his heart was found to be enlarged, but no ætiological diagnosis was made, beyond the possibility of cardiac amyloidosis.

From 1948 until early 1954 his main complaints were of constant fatigue and slight dyspnœa on effort. The attacks of faintness were characterized by a very rapid heart action for a few seconds, followed by transient loss of consciousness, recovery occurring rapidly with no after-effects. Observed during one of these attacks, his pulse rate rose to over 150, with an apparently regular rhythm but a very small pulse volume. The rate fell to 60 in a few seconds, and he recovered consciousness. Unfortunately, we were unable to obtain any electrocardiograms during these attacks.

On examination, the liver was just palpable and firm, but no other evidence of congestive cardiac failure was found, and he was not cyanosed, either at this stage or later. The heart rhythm was regular and 80 a minute. The brachial blood pressure was 110/90 mm. The apex beat was just palpable in the mid-axillary line, in the sixth interspace; no præcordial pulsation was seen or felt, and no thrills were palpated. The heart sounds were noted as being very quiet, no murmurs or added sounds were heard, and there were no abnormal signs in the lungs.

The electrocardiogram showed sinus rhythm with ventricular ectopic beats, evidence of right atrial hypertrophy, and a partial right bundle-branch block. Chest X-ray (Fig. 1) and radioscopy revealed an enormous heart, with a narrow vascular pedicle, a concavity in the region of the pulmonary conus, and what appeared to be enlargement of the right atrium, and both ventricles. Pulsation was present but much diminished along the whole contour, and the œsophagus was not displaced. The lungs were oligæmic.

A tentative diagnosis of constrictive pericarditis was made, although many anomalous features were present, and thoracotomy was undertaken in July, 1954. On exposing the heart, a normal pericardium was found, but the right and left ventricles could not be identified, although the impression of the surgeon at the time was that the chamber he could palpate anteriorly was the right ventricle. Post-operative recovery was uneventful, but a year after operation the first signs of severe congestive cardiac failure appeared, and worsened until in May, 1956, he was readmitted with marked ascites and œdema of his legs, back, and genitalia. The jugular veins were filled to a level 8 cm. above the sternal angle, but no pulsation could be observed. The liver, palpated after the ascites had been drained, was firm, painless, and did not pulsate.

The pulse was of very poor volume, the rhythm completely irregular, and the systolic blood pressure was 110 mm. Hg. The apex beat was just palpable, now in the posterior axillary line. The heart sounds were irregular but otherwise unchanged, and there was no evidence of pulmonary œdema. The radioscopic appearances were as before, but his electrocardiogram from this time onwards showed varying arrhythmias, with atrial flutter, atrial fibrillation, and ventricular ectopic beats.

Reappraisal of the diagnosis led us to believe that this man had an Ebstein's anomaly, the evidence in favour being the enlarged, quietly acting heart, the episodes of paroxysmal tachycardia, the electrocardiographic findings, and the oligæmic lung fields. Cardiac catheterization was, therefore, not performed.

A more prolonged attack of unconsciousness occurred on December 28, 1956, from which the patient did not recover. No medical attendance was forthcoming until after death, but presumably he had a more prolonged and fatal attack of tachycardia.

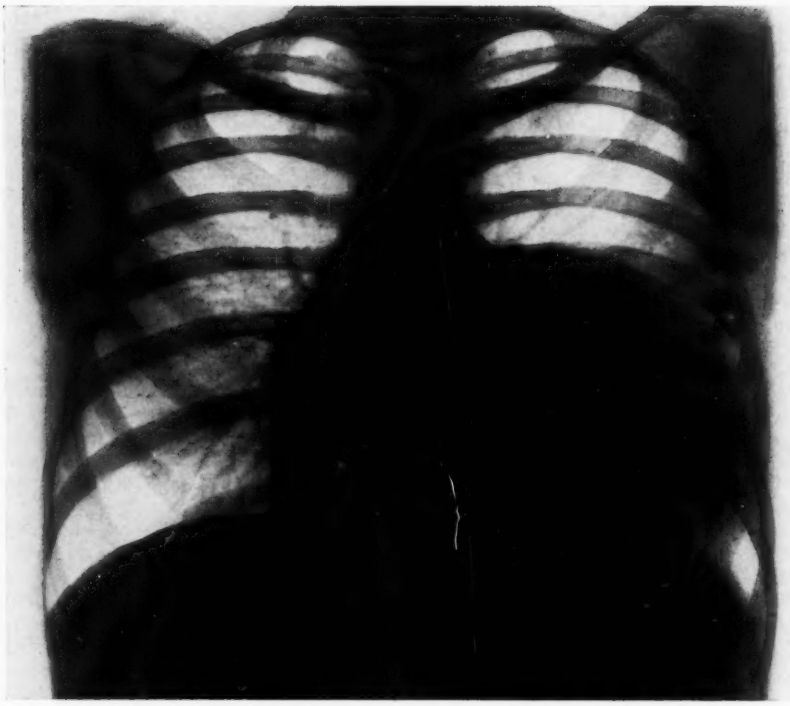


FIG. 1.—Postero-anterior radiograph, showing the enlarged heart, and oligæmic lung fields.

Necropsy was performed two days later. The liver showed severe cardiac cirrhosis, and gross ascites was present. Extensive dissection of both lungs showed no macroscopic abnormality, all the pulmonary vessels being normal. No fluid was present in the pleural cavities.

The heart (Fig. 2) weighed 580 g. and occupied a large proportion of the left hemithorax. Inspected *in situ*, the left ventricle could not be identified, but after removal of the whole organ, the left atrium and ventricle were seen posteriorly. Both chambers were slightly dilated, and the wall of the left ventricle was 12 mm. thick. Over the apex and adjoining septum of the left ventricle, the endocardium was opaque, white and thickened, sections of this area showing definite subendocardial fibrosis. The same appearances were present in the left atrium. The mitral and aortic valves were normal, the foramen ovale was sealed, and the septa were intact. The coronary arteries were normal in every respect.

The right atrium was dilated, with an approximate capacity of 350 ml. The wall was hypertrophied and much mural thrombus was present in the atrium itself and its appendage. Both venæ cavæ were normal, as was the coronary sinus. The tricuspid valve ring was normally situated, but was dilated to 19·5 cm. Only two cusps were found, the postero-septal and the anterior. They were of normal texture, but short, with the postero-septal valve adherent to the ventricular wall, and the chordæ tendineæ were poorly developed and very fine. In a similar fashion, the papillary muscles were underdeveloped. The valve was certainly incompetent, as the shortened cusps clearly could not meet. The right ventricle was grossly dilated and thin, being almost translucent in places. The trabeculæ in the chamber were very numerous, forming a dense and complicated network. The pulmonary valve ring was normal, as were the cusps.

The endocardium over the anterior surface of the ventricle was thick and white, sections showing very few muscle fibres in this area, with dense subendocardial fibrosis. This was thought to be an old organized mural thrombus, a more recent, flat, laminated mural thrombus being present just beneath the anterior cusp of the atrioventricular valve, the deeper layers of this area being similar to the section showing the subendocardial fibrosis.

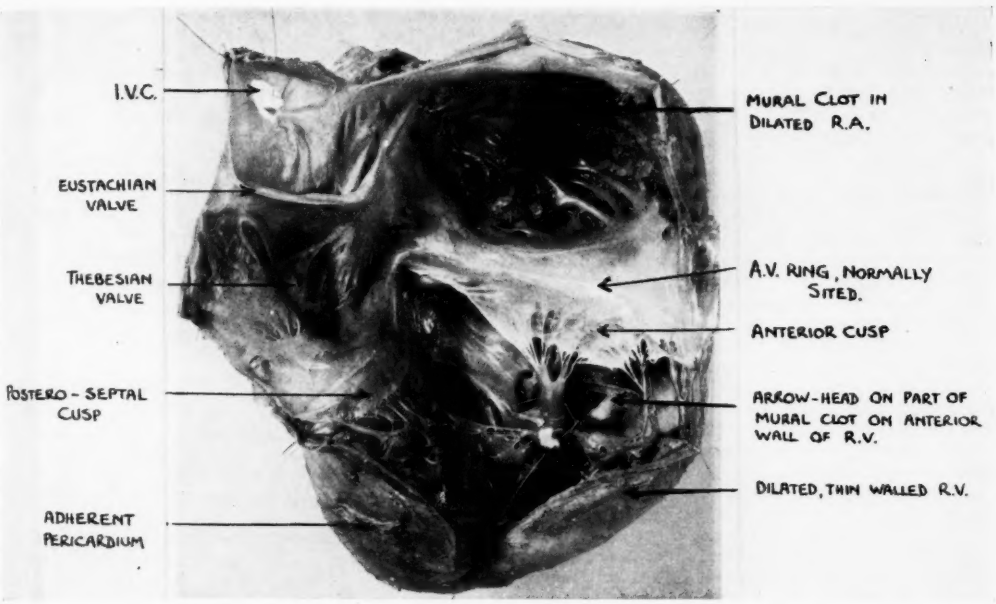


FIG. 2.—Photograph of the opened right atrium and ventricle, showing the greatly enlarged right atrium, the thin-walled ventricle, the bicuspid right atrio-ventricular valve, and the greatly dilated valve ring.

Discussion and Summary

The necropsy showed that this was a case of congenital bicuspid right atrio-ventricular valve, with gross dilatation of a normally-sited valve ring, different from the Ebstein malformation in that the posterior cusp could not be identified. The right ventricle had not hypertrophied, although presumably the regurgitation through the atrio-ventricular valve had been present from birth. On the contrary, the ventricle had stretched and become thin under the load, but this may have been due to a congenital defect of the muscle itself. The subendocardial fibrosis has not been described in this condition before, although it is an accepted finding in Ebstein's anomaly.

Barritt and Urich (1956) found six previously reported cases and added one of their own, only three of the seven cases being over one year old, and only three having a bicuspid right atrio-ventricular valve. None of these patients were described as having dilatation of the right ventricle, with thinning of the walls, and none had subendocardial fibrosis.

Moreover, the case described here had no murmurs to suggest the presence of tricuspid incompetence. There was no abnormal jugular pulsation, and the liver was never found to be pulsatile. All these features were probably due to the weakness of right ventricular systole. In fact, the clinical picture appeared typical of Ebstein's anomaly, with the abnormally quiet heart sounds, no visible or palpable right ventricular lift, no murmurs, and oligæmic lung fields. The electrocardiographic findings and the paroxysmal arrhythmias, too, appeared typical.

I would like to thank Dr. E. Noble Chamberlain and Dr. E. Wyn Jones for allowing me to publish this case, Dr. J. Carr Brundret for the performance of the autopsy, and Dr. R. E. B. Hudson for the photograph in Fig. 2, and for his great help in elucidating the autopsy findings.

Reference

Barritt, D. W., and Urich, H. (1956). *Brit. Heart J.*, **18**, 133.

ABSTRACTS OF CARDIOLOGY

Edited in collaboration with Abstracts of World Medicine

De Motu Cordis. By WILLIAM HARVEY, translated from the original Latin by KENNETH J. FRANKLIN. Pp. xii and 209. Price 17*s.* 6*d.* Blackwell Scientific Publications: Oxford.

This new translation of *De Motu Cordis* by Professor Franklin, prepared at the invitation of the Royal College of Physicians, was published in 1957 as a contribution to the commemoration of the tercentenary of Harvey's death. The aim of the translator was "to get nearer to him in thought by attempting to discover more precisely what he intended to convey by every latin sentence that he included in the great work of 1628" and all students of the circulation will be grateful to Professor Franklin for this work. His new translations of the rest of Harvey's published works on the circulation will be eagerly anticipated. *Graham Hayward*

Classics in Arterial Hypertension. By ARTHUR RUSKIN, M.D., F.A.C.P. Pp. xxv and 358. 72*s.* Blackwell Scientific Publications: Oxford.

This history of hypertension is divided into two parts: the first, on methods of measurement of blood pressure, ranges from the papers of Stephen Hales (1733) to Korotkov (1905), and the second, on the significance of hypertension, from Aurelianus (400) to Goldblatt (1934). The selection of original papers and excerpts includes several that are not generally recognized in historical surveys of this disease and the text is illustrated with portraits and many original figures. The publication of this attractive work in the American Lecture Series is most welcome at the present time when so much attention is being paid to the disease. *Graham Hayward*

Pediatric Cardiology. By ALEXANDER NADAS, M.D., F.A.A.P. Pp. xxii and 587. 84*s.* London: W. B. Saunders Co. Ltd.

With the exception of arteriosclerotic heart disease this book by Dr. Nadas includes most of the cardiovascular diseases that may be encountered in adult patients. The natural history of these diseases extends in most cases over a much longer period of time than the first one or two decades and it is difficult for a pædiatrician to give a balanced account of many types of heart disease in children when this is so much influenced by what happens after they have outgrown the children's clinic. For this reason the sections on course and prognosis in this book are brief and less satisfactory than the clinical accounts of the cardiovascular diseases of children which are excellent. The emphasis is on clinical management but the author has made full use of modern physiological methods of investigation to increase the accuracy of clinical diagnosis and has produced a handbook that will be of great interest not only to the pædiatrician and general physician, for whom it was written, but also to the cardiologist. One criticism of the production of the book is the poor quality of reproduction of the cardiograms many of which are indecipherable and several mounted upside down. *Graham Hayward*

Surgery of the Open Heart. By CH. DUBOST and PH. BLONDEAU. Pp. 320. Price 3,000 fr. Paris: Masson et Cie.

This monograph surveys the various methods that are at present available for the surgery of the open heart. The first part deals with operations under hypothermia and the second the use of an extra-corporeal circulation. A great part of the book is devoted to technical descriptions of the various types of apparatus which are in use, but the authors also discuss physiological principles and the difficulties encountered in both these methods of open heart surgery. The actual surgery of the heart itself and the more clinical aspects of the subject are discussed very briefly and the chief value of this book is in providing a review of present established and experimental technical methods. *Graham Hayward*

Pulmonary Function in Left Ventricular Failure, Including Cardiac Asthma. R. S. COSBY, E. C. STOWELL, W. R. HARTWIG, and M. MAYO. *Circulation* (*N.Y.*), **15**, 492–501, April, 1957.

An extensive study of pulmonary function in 8 patients with hypertensive heart disease in congestive failure and cardiac asthma was carried out at the University of South California School of Medicine and the County Hospital, Los Angeles, the findings being compared with those in 14 patients with mitral stenosis and congestive failure and 16 patients with emphysema and right heart failure. The patients were selected because of severe dyspnœa, irrespective of the presence of a "wheeze", and were bedridden at the time of examination. The procedure included measurement of lung volume, and analysis of blood and gas distribution in the lung, as well as measurement of diffusing capacity by the technique of Riley *et al.* (*J. appl. Physiol.*, 1951, **4**, 102). In some patients arterial oxygen saturation following positive-pressure breathing exercise and inhalation of 100% oxygen was estimated. The expiratory air-flow pattern was analysed by recording a pneumotachogram and simultaneously determining the oxygen and carbon dioxide tensions in the expired gas, an infrared analyser and a Beckman mass spectrometer being used.

The lung lesion in patients with hypertensive congestive heart failure was found to resemble that in emphysematous patients, but to differ from that in patients with cardiac failure from rheumatic heart disease, there being a definite obstructive type of ventilatory defect with

reduced vital capacity and maximum breathing capacity in hypertensive congestive heart failure. In hypertensive patients, again as in those with emphysema, the peripheral blood showed increased tension of carbon dioxide in contrast to the lowered carbon dioxide tension in patients with rheumatic heart disease, although in the latter group there were greater abnormalities of diffusion than in the hypertensive group. The emphysematous patients differed from those with hypertensive heart failure in showing a much greater transfer gradient and percentage venous admixture. *P. Hugh-Jones*

Hyperaldosteronism in Heart-disease. H. P. WOLFF, K. R. KOCZOREK, and E. BUCHBORN. *Lancet*, **2**, 63–66, 1957.

The urinary excretion of aldosterone and sodium in 40 patients with various forms of heart failure and 30 healthy subjects have been meticulously studied. The values for urinary excretion of sodium and aldosterone in healthy subjects with and without a restricted dietary intake of 60 to 80 mEq. of sodium daily served as control readings for similar estimations in 8 patients with left ventricular failure, 7 with right-sided cardiac failure, 21 with pulmonary and systemic congestion, and 4 patients examined within a week after myocardial infarction, all of whom were studied before treatment and again after digitalization, salt restriction, and administration of diuretics.

In the patients with left-sided failure the excretion of aldosterone and of sodium was usually normal, whereas most patients with right-sided failure showed increased aldosterone activity and considerable sodium retention. During treatment with a salt-restricted diet, digitalis, and diuretics the response was variable. When diuresis was induced by mercurial diuretics or carbonic anhydrase inhibitors the excretion of aldosterone increased considerably within one to three days.

D. Geraint James

The Significance of Lymphatic Circulation in Certain Internal Organs. I. RUSNJAK. *Ter. Arkh.*, **29**, 5–16, No. 6, June, 1957.

The flow of lymph in the internal organs, which is not dependent on movement as in the extremities, is in some cases very large; for example, the daily lymph flow through the kidneys is equal to the volume of urine excreted, and that through the liver is nearly as great. The author reports the results of animal studies in which the efferent lymphatics of the heart, lungs, alimentary tract, liver, and kidneys were occluded experimentally.

These showed that lymph from the two sides of the heart drains into two separate lymph vessels and eventually enters the circulation via the thoracic duct or the right lymphatic duct. Electrocardiographic (EC) recordings from such hearts showed departures from normality which were not found in control animals subjected to thoracotomy but without ligation of the lymphatics. These changes were of three types: (1) the S–T segment was depressed and the T waves flattened; (2) the appearances were those of myocardial infarction; (3) the recordings were characteristic of an acute and severe cardiac anoxæmia. Histologically, interstitial œdema of the myocardium and dilatation of lymph capillaries was found post mortem with, in 3 cases, areas of focal necrosis of heart muscle. While ligation of the lymph vessels or of the coronary sinus alone was in many cases not fatal and the EC tended eventually to become normal, the combined occlusion of coronary sinus and lymphatics was inevitably fatal in from 3 hours to 6 days; in these latter cases hæmorrhagic necrosis of the heart muscle was found.

In the case of the lungs and liver, in which the venous pressure is much lower and the lymph has a much higher protein content, ligation of the efferent lymphatics produced œdema in the same way as in the heart. This œdema was found to be much more severe in the presence of pulmonary hypertension due to mitral disease, as shown by experiments on 8 dogs in which mitral incompetence (6 cases) or stenosis (2 cases) had previously been produced by operation. Simultaneous ligation of the lymphatics and of the common bile duct caused still greater œdema.

In the same way ligation of the renal efferent lymphatics produced œdema, but if this was accompanied by simultaneous ligation of the ureter there ensued serious necrotic changes.

It is evident that the study of the circulation of lymph in the internal organs in normal and in pathological conditions is of great importance—much greater than has hitherto been supposed—and that further investigations will throw light on many conditions which are at present obscure.

[This is a most stimulating and thought-provoking paper, to which an abstract can do but little justice.]

L. Firman-Edwards

Diagnostic and Prognostic Significance of Serum Transaminase Levels in Coronary Occlusive Disease. A. A. KATTUS, R. WATANABE, and C. SEMENSON. *Circulation* (*N.Y.*), **15**, 502–511, 1957.

The authors discuss their findings in 255 patients aged 37 to 85 years (all except 3 being males) who were admitted because of chest pain strongly suggestive of myocardial infarction. These findings confirm that a rise in the serum glutamic oxalacetic transaminase (SGO–T) level, starting some hours after the onset of pain, reaching a peak in 24 to 48 hours, and then gradually falling to normal over the following 3 or 4 days, is of diagnostic importance in myocardial infarction, and that the extent of the rise may be of prognostic significance. Of the 255 patients, 111 were considered to have proven infarction from the history, the clinical evidence, and the changes in the electrocardiogram; in all these 111 cases the SGO–T levels, as estimated serially over the first 3 to 6 days after the onset of pain, were raised. In 144 cases the electrocardiogram was not diagnostic of infarction; in 63 of these there was a rise in the SGO–T level compatible with infarction. At necropsy in 7 cases in this last group infarction was found.

[A number of recent papers have presented similar findings. Estimation of the glutamic oxalacetic transaminase liberated from the damaged heart muscle seems to be of value in the differentiation of infarction from angina and of cardiac from pulmonary infarction.]

P. Hugh-Jones

Circulatory Studies in Hypertensive Patients at Rest and during Exercise. With a Note on the Starling Relationship in the Left Ventricle in Essential Hypertension. S. H. TAYLOR, K. W. DONALD, and J. M. BISHOP. *Clin. Sci.*, **16**, 351, 1957.

In the study reported here from the Queen Elizabeth Hospital, Birmingham, the authors have investigated the hæmodynamics of 20 patients with essential hypertension by means of cardiac catheterization. The patients were divided into two groups according to their degree of exercise tolerance and, under mild sedation, the values for various hæmodynamic factors were determined, first at rest and then during the fourth or fifth minute of exercise which was approaching the limit of tolerance. No patient showed any clinical evidence of right or left ventricular failure at the time of the study, and none was receiving hypotensive drugs. Control values were those obtained in a previous study of 16 normal subjects under similar conditions.

The less disabled patients did not differ significantly from normal, and during exercise they showed a normal response in regard to cardiac output, except that in the majority of cases there was a significant rise in pulmonary wedge pressure. In the second group, however, that is the more disabled patients, the oxygen uptake was higher than normal and the cardiac output lower at rest. They showed an abnormal rise in pulmonary wedge pressure on exercise and in some this pressure was high even at rest. Exercise produced a subnormal response in cardiac output in all cases in this group.

The relationship of the left ventricular filling pressure to ventricular work in this series of patients is compared with that found by Starling in the isolated dog heart.

J. Warwick Buckler

Hypertension Due to Unilateral Renal Disease—with a Report on a Functional Test Helpful in Diagnosis. T. B. CONNOR, M. BERTHRONG, W. C. THOMAS, and J. E. HOWARD. *Bull. Johns Hopk. Hosp.*, **100**, 241–276, 1957.

In this paper the authors describe their investigation of a possible method of distinguishing those cases of hypertension that are associated with unilateral renal disease and in which nephrectomy might be expected to cure the hypertension. In principle, the method consisted in collecting simultaneous samples of urine from each kidney by ureteric catheterization and measuring their volume and sodium concentration.

In 31 patients with essential hypertension and normal kidney function the specimens of urine from the two kidneys were virtually identical in volume and sodium concentration. In 11 patients with hypertension and presumed bilateral kidney disease ureteric catheterization frequently showed marked differences in the volume of urine excreted by the two sides, but the sodium concentration in the specimen from the kidney secreting the greater volume of urine was always either equal to or less than that in the specimen from the other kidney. In a further group of 4 patients with severe hypertension, 2 of whom had arteriographic evidence of unilateral renal disease, one kidney consistently excreted less urine with a lower sodium concentration than the other. In each case nephrectomy improved the hypertension, one of the excised kidneys showing only hypertrophy of the juxtaglomerular apparatus, but the other 3 containing areas of "ischæmic" tubular atrophy. In another group of 4 patients with hypertension there was pyelographic evidence of unilateral kidney disease, but in none of these was the hypertension relieved by nephrectomy. Ureteric catheterization studies in these cases had revealed differences in the volume and sodium concentration of the urine from the two sides, but in no case did the lesser sodium concentration correspond with the smaller volume of urine. In 15 cases with similar findings nephrectomy was not carried out.

The course of hypertension was also observed in 10 cases following the removal of a completely non-functioning kidney. In 7 of these the rapid onset of severe, progressive hypertension, or an abrupt increase in previously mild hypertension, were outstanding clinical features. Retrograde pyelography showed a normal collecting system on the affected side in 7 cases, this finding being considered to indicate a renal vascular accident as the cause of the loss of function. Of the 10 patients, 8 derived marked benefit from nephrectomy, the follow-up period ranging from one to $4\frac{1}{2}$ years.

The histological findings in kidneys removed at operation in cases of hypertension are discussed and the authors advance the view that the essential feature of hypertension of renal origin is "ischæmic" atrophy of significant numbers of convoluted tubules which still contain apparently functional tubular cells, as opposed to the thyroid-like tubules with extreme atrophy of the epithelium which are seen in advanced cases of pyelonephritis.

[This is a most stimulating paper which will repay reading in the original.] *H. F. Reichenfeld*

The Significance of Nonbacterial Thrombotic Endocarditis: an Autopsy and Clinical Study of 78 Cases. R. A. MACDONALD and S. L. ROBBINS. *Ann. intern. Med.*, **46**, 255, 1957.

In the opinion of the authors not enough importance is attached to the finding of non-bacterial thrombotic endocarditis at necropsy. Often referred to as terminal endocarditis, it is considered by many to be a terminal condition and without clinical significance. In support of their view the authors describe 78 cases of the condition found during the course of 18,486 consecutive post-mortem examinations over 22 years at the City Hospital, Boston, Massachusetts. Of the 78 cases, 40 were in men and 38 in women ranging in age from 18 to 90 years, 69 of the patients being over 49. The chief underlying diseases in these cases were cancer, heart failure, and vascular thromboses. The mitral valve was most commonly affected, and the condition had to be distinguished from the other common types of endocarditis—bacterial and rheumatic. Important for histological differentiation is the fibrocollagenous degeneration of the valve with a relative lack of cellular infiltration of the valve beneath the thrombus. An important clinical point that emerges from this study is that in 11 of the 78 cases there was evidence of multiple peripheral emboli which presumably came from the diseased valve.

G. S. Crockett

A Study of the Cardiovascular Changes during Cooling and Rewarming in Human Subjects Undergoing Total Circulatory Occlusion. E. BLAIR, R. R. AUSTIN, S. G. BLOUNT, and H. SWAN. *J. thorac. Surg.*, **33**, 707–718, 1957.

The authors of this paper from the University of Colorado School of Medicine, Denver, claim that it is the first to report direct measurements of arterial and central venous blood pressures made during cooling, total circulatory occlusion, and rewarming in patients undergoing open cardiotomy during hypothermia. Adequate data were obtained on 23 patients ranging in age from 3 to 35 years, all of whom were suffering from congenital disease of the heart. After induction of anæsthesia with ether the patients were cooled to 26° to 31° C. by immersion in cold water; rewarming was aided by diathermy.

During cooling, blood-pressure sounds became inaudible between 31° and 37° C., and later the pulse became impalpable. At the moment of disappearance of the Koratkov sounds the intra-arterial blood pressure was found to be adequate, being in all cases above 73/51 mm. Hg, and in one case as high as 155/103 mm. Hg. However, the blood pressure continued to fall for some time after the attainment of the lowest temperatures, reaching a mean value of 60 mm. Hg between 26° and 29° C. The pulse pressure was not greatly reduced and pulse rates slowed to an average value of 60 per minute. Central venous pressure was raised during hypothermia. During total circulatory occlusion the blood pressure did not fall to zero but, after one to two minutes, was usually stabilised above 20 mm. Hg. The cause of this "cadaveric" pressure was not apparent. The heart rate lay between 20 and 84 beats per minute, but was clearly influenced both by coronary perfusion of neostigmine and by the surgeon's manipulations. The central venous pressure was further elevated during the occlusion. On the release of occlusion 6 patients showed an overshoot of blood pressure, 2 with an accompanying fall in pulse rate. Within a few minutes conditions had returned to pre-occlusion levels, and the phenomenon of overshoot did not appear to be related to the duration of the occlusion. In the rewarming phase the pulse and blood pressure reappeared at lower temperatures than those at which they had disappeared, and at a temperature of 34° C. the circulatory signs had returned to within normal limits in all the patients studied.

The authors conclude that the cardiovascular reflex mechanisms regulating the circulation are intact in the range of hypothermia studied (26° to 31° C.). The clinical disappearance of pulse and Koratkov sounds is attributed to constriction of the larger arteries and not to any change in the pulse pressure, which appears to remain normal. *J. F. Nunn*

A Simple Test for Interatrial Communication. G. DE J. LEE and T. M. D. GIMLETTE. *Brit. med. J.*, **1**, 1278, 1957.

The authors, working at St. Thomas's Hospital, London, have developed a simple and safe test for atrial septal defect that depends upon altering pressures in the atria separately, thereby changing the blood flow across the septal defect. Alterations in arterial oxygen saturation are then detected by the ear oximeter. The method requires continuous recording of arterial oxygen saturation, intrathoracic pressure (via an intra-œsophageal catheter), and brachial arterial pressure with the patient in the sitting posture. The patient carries out Valsalva's manœuvre at rest and after exercise. During Valsalva's manœuvre the intrathoracic pressure rises and the net right atrial pressure (right atrial pressure minus intrathoracic pressure) falls. After Valsalva's manœuvre the net right atrial pressure rises higher than its resting level, inducing a right-to-left shunt for a few seconds which is detected by the ear oximeter.

The Valsalva test gave a positive result in 12 cases of atrial septal defect proven at operation or by passage of a catheter across the defect; in 11 of them the result was positive at rest, and in the 12th case it was positive only after exercise. A positive result was obtained in 14 cases of probable atrial septal defect with catheter evidence of left-to-right shunt at atrial level. The test gave a negative result in 2 patients with partial anomalous pulmonary venous drainage but without atrial septal defect and in one patient with ventricular septal defect. In 2 patients with atrial septal defect and heart failure there was a negative finding with the Valsalva test, but both Muller's manœuvre and elevation of the legs led to shunt reversal and fall in atrial oxygen saturation. *K. G. Lowe*

Hypertrophy of the Right Ventricular Outflow Tract. A Concept of the Electrocardiographic Findings in Atrial Septal Defect. S. G. BLOUNT, E. A. MUNYAN, and M. S. HOFFMAN. *Amer. J. Med.*, **22**, 784–790, May, 1957.

In this communication evidence is presented to support the concept that the rSR′ pattern with a total QRS time of 0·08 to 0·10 second seen in certain congenital and acquired cardiac lesions—but predominantly in atrial septal defect—is due to hypertrophy of the right ventricular outflow tract rather than to incomplete right bundle-branch block. Thus recordings from direct epicardial leads during operations on patients with atrial septal defect revealed that rSR′ or rSR′s′ patterns were obtained only from the right ventricular outflow tract, while RS patterns were obtained from the mid-right ventricle. This observation correlated well with intracavitary electrocardiograms taken during catheter withdrawal. Further evidence in favour of this concept was the gradual transition of an obvious pattern of right ventricular hypertrophy in cases of valvular pulmonary stenosis to rSR′ and finally rSr′ patterns following surgical correction. The findings in patients after operation for relief of mitral stenosis and atrial septal defect were also in accord with the concept. As the authors point out, the acceptance of this concept does not mean that this pattern cannot be exactly duplicated by incomplete right bundle-branch block, as evidenced by a tracing reproduced in the paper. *William A. R. Thomson*

The Prognosis of Atrial Septal Defect. M. CAMPBELL, C. NEILL, and S. SUZMAN. *Brit. med. J.*, **1**, 1375–1383, 1957.

The diagnosis and clinical course of atrial septal defect and the prognosis in this condition are discussed in this

paper, with reference to the findings in 100 patients, in two-thirds of whom the diagnosis was proved at cardiac catheterization or necropsy. The commonest errors in diagnosis were failure to detect mild pulmonary stenosis or to recognize that a large septal defect might be ventricular. Absence of wide splitting of the pulmonary second sound and evidence of left ventricular hypertrophy suggest ventricular septal defect. In 12 patients there was associated pulmonary stenosis and the physical signs were mainly those of this lesion, even when it was the minor lesion, although screening showed increased pulmonary arterial pulsation. About one-tenth of the patients had anomalous pulmonary venous drainage; none had a "cottage-loaf" heart.

Discussing the course and prognosis in age groups, the authors state that most infants with atrial septal defect survive, but occasionally a large defect causes death in an infant. Patients in the first two decades lead nearly normal lives, although they have large hearts, 95% doing well at age 20 and 85% at age 30. Only about half the patients seen at hospital are still well at age 40, and less than a quarter at age 50, but these figures for adults are drawn from a selected population. In early childhood the electrocardiogram usually shows the rSR′ pattern. Generally, the heart is large and, having reached a position of equilibrium, remains about the same size until the age of 25 to 35. In the third decade some patients have increasing dyspnœa, up to one-third may lose ground seriously, and atrial fibrillation, pulmonary regurgitation, and reversal of the shunt appear. By the fourth decade most of the patients have become severely disabled (of 11 so disabled in the authors' series, 6 died). Disablement occurs most commonly from right heart failure without much pulmonary hypertension, and less commonly from pulmonary hypertension with reversal of the shunt, central cyanosis, and right heart failure or pulmonary arterial thrombosis. The onset of atrial fibrillation in these cases is serious. The average age at death in the present series was 39, the commonest cause being right heart failure or pulmonary infarction, but the authors cite cases and an additional case of their own in which active life was still possible in the fifth and sixth decades.

[This important paper should be consulted in the original.] *D. Emslie-Smith*

Patent Ductus Arteriosus with Reversal of Flow. Clinical Study of Ten Children. R. C. ANDERSON, P. ADAMS, and R. L. VARCO. *Pediatrics*, **18**, 410, 1956.

The clinical features in 10 cases of patent ductus arteriosus with reversal of flow are described. The patients, all children, had cyanosis, often greater in the toes, and dyspnœa on exertion had developed early in life. The electrocardiogram showed right ventricular hypertrophy in all cases. Cardiac catheterization indicated bidirectional shunt through the duct in 6 cases; in one case there was a reversed shunt flow only, while in 3 the data did not permit a definite conclusion to be reached.

Ligation of the patent ductus was successfully accomplished in one instance with significant clinical improvement. In 2 other cases ligation was followed by irreversible cardiac arrest.

The authors review 45 repeated cases, the majority of which were in adults. In 22 of these surgery was performed, with good results in 4. In their view surgical treatment is likely to be disappointing in adults, but may be more successful when carried out early in life.

Gerald R. Graham

Studies of Function in Anastomosis of the Superior Vena Cava with the Right Pulmonary Artery. T. M. DARBINIAN. *Sovetsk. Med.*, 28–32, April, 1957.

The author reviews the various attempts that have been made at anastomosis of the superior vena cava with the right pulmonary artery in the treatment of pulmonary stenosis.

He states that Meshalkin in 1956 carried out a series of such operations at the Vishnevskii Institute with good results. This method avoids one drawback of the Blalock–Potts operation, namely, that it does not lead to a "repeat circulation" through the pulmonary circuit; moreover, it can be employed in pulmonary and tricuspid atresia. The technique, which is simple and obviates intracardiac manipulation, is especially suitable in cases of Fallot's tetralogy and of atresia of the opening of the superior vena cava. *L. Firman-Edwards*

Chest Pain in Patients with Isolated Pulmonic Stenosis. R. P. LASSER and G. GENKINS. *Circulation* (*N.Y.*), **15**, 258, 1957.

At Mount Sinai Hospital, New York, the authors have observed 5 patients with congenital isolated pulmonary stenosis and typical angina pectoris or acute prolonged coronary insufficiency, but without frank evidence of myocardial necrosis. In all the patients the cardiac ischæmic pain was relieved by pulmonary valvotomy. In a discussion the authors state that the pain is due to right ventricular myocardial ischæmia, and that the factors that impair coronary circulation are: (1) very high right ventricular intracavitary systolic pressure and prolongation of right ventricular systole; (2) fixed low cardiac output; and (3) high right atrial and ventricular diastolic pressures which reduce the coronary arteriovenous pressure gradient. *K. G. Lowe*

The Clinical Aspects of Arteriosclerosis. By SEYMOUR H. RINZLER, M.D., F.R.C.P. Pp. xiii and 339. Price £3 6*s*. Blackwell Scientific Publications: Oxford.

After a short introductory chapter, which summarizes the present state of knowledge concerning the pathogenesis of arteriosclerosis, this book consists of an account of the effect of this disease on the heart, brain, and peripheral vessels. The actual clinical aspects of the arteriosclerotic diseases are discussed very briefly and the chief value of the book is the excellent survey the author has made of the enormous number of books and papers that have been written on the subject, with particular reference to diagnosis and methods of treatment. The book is useful more as a review than as a practical manual for the diagnosis and treatment of arteriosclerosis. *Graham Hayward*

THE ORIENTATION OF THE HEART AND THE APPEARANCE OF ITS CHAMBERS IN THE ADULT CADAVER

BY

ROBERT WALMSLEY

From the Department of Anatomy, St. Salvator's College, University of St. Andrews

Received January 30, 1958

The gross anatomy of the heart has been studied for hundreds of years and doctors have long been familiar with its main features. Developments in clinical practice in the last 25 years and particularly in the last decade demand, however, a detailed knowledge of certain aspects of cardiac anatomy that is not always available in current text-books. This is apparent if one considers the necessity for the radiologist or clinician screening cardiac patients to be familiar with the detailed anatomy of the various chambers and vessels whose shadows he is inspecting. Again the surgeon engaged on intracardiac surgery must be familiar not only with the gross anatomy of the cardiac chambers but with the minute anatomy, location, and relations of the valve cusps. The clinician at the bedside is helped in his understanding of physical signs by the ability to visualize the chambers of the heart in their proper relationship to one another and their orientation within the thorax.

It seemed apposite therefore, to re-investigate the anatomy of the heart by examining it *in situ*. A series of sections of entire thoraces were made and studied, some of them having been cut transversely and others in the two oblique planes that allowed the form of the heart and the great vessels to be compared with the right and left anterior oblique views as seen on radioscopy. The primary purpose of this paper is to illustrate and comment on selected sections cut in these planes, but no attempt is made either to review all aspects of the gross anatomy of the heart, or to discuss the distortion that may occur in it as the result of pathological changes.

Right Heart and Left Heart

The terms "right heart" and "left heart" are commonly used in clinical practice and developmentally these terms are correct and indicate precisely the relationship of the right chambers to those of the left in the young embryo.

In the 10 mm. human embryo, for example, when the septum primum of the atrial septum is well established and the muscular part of the ventricular septum has appeared, the heart is an almost symmetrical structure: the two right chambers lie directly to the right of those of the left heart, and the septa between the atria and between the ventricles lie almost in the mid-line (Fig. 1).

Throughout development and even into adult life, the atrial and ventricular septa remain approximately "in line" with each other and thus allow a plane, which is here referred to as the "plane of the septa", to be defined. The plane of the septa is considered as being indicated by a line which passes from the anterior interventricular groove (or the associated artery if the groove is not evident) to the posterior attachment of the atrial septum. This line sometimes passes through the substance of the ventricular septum but frequently lies along the right face of this septum.

It is not proposed in this communication to consider the details of the rotation of the heart nor the factors that may be involved in it, but certain facts would appear to be relevant. The first of these is that rotation commences shortly after the 10 mm. stage so that the anterior interventricular sulcus is displaced towards the left and the posterior attachment of the atrial septum towards the right, and in consequence the right heart comes to lie not only to the right of the left heart but to an

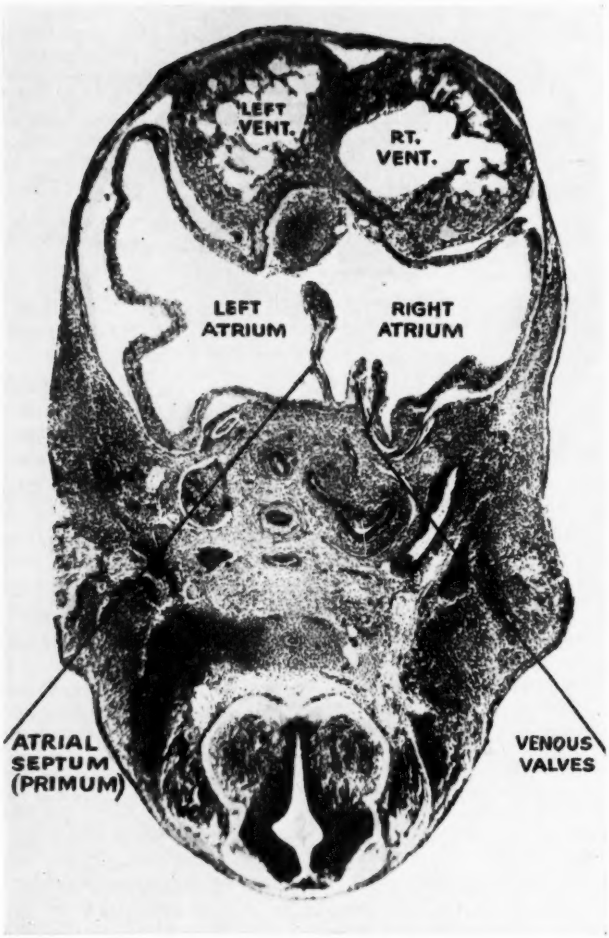


FIG. 1.—Transverse section of thorax of 10 mm. human embryo. The septum primum partially separates the right and left atria (an ostium primum being present) and in this particular section the two ventricles are seen to be completely separated by the muscular part of the ventricular septum. The septa lie almost in the midline and the chambers comprising the right heart therefore lie directly to the right of those of the left heart. Conventionally an embryo is featured with its dorsal surface uppermost and its ventral surface downwards but in order to maintain uniformity among the figures of this article this embryo is shown with its dorsal surface directed towards the foot of the page. The right side of the embryo is therefore on the reader's right and the left side on his left. Magnification, × 150.

increasing degree, in front of it. In the 4½ months fœtus (Fig. 2) the plane of the septa has attained an obliquity which is at an angle of about 45° to the median plane, and this is the approximate angulation that has been encountered in all older fœtal and adult specimens in which the heart has been sectioned *in situ*. All observations have led me to the conclusion that rotation of the heart occurs early in development and is completed during the first half of intra-uterine life. This is not in keeping with statements such as that of Baxter (1953) where it is claimed that the rotation does not occur till "towards the end of intra-uterine life".

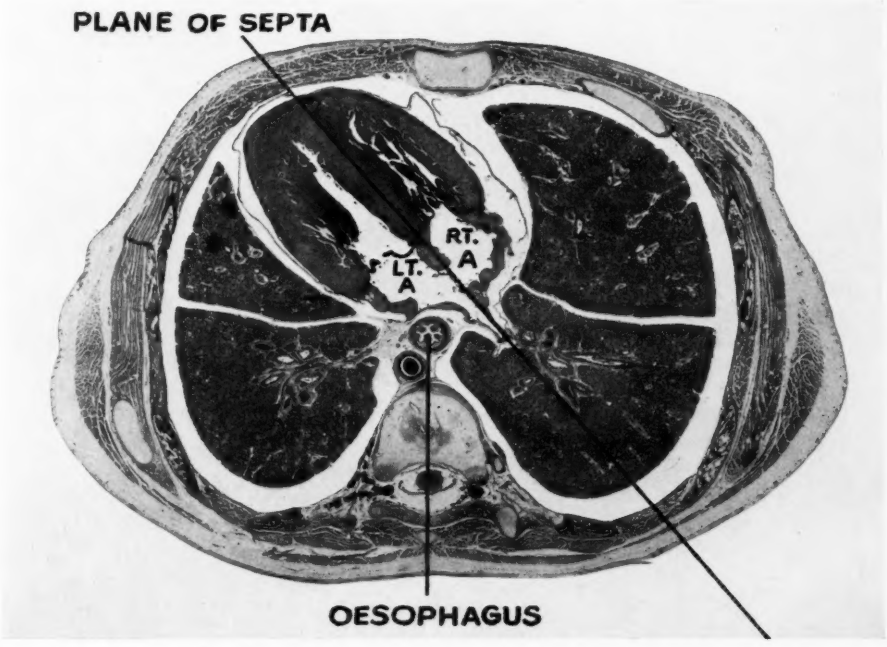


FIG. 2.—Transverse section of thorax of 125 mm. (4½ month) human fœtus. The heart by this stage has assumed an orientation which is characteristic of the adult. As the line of the septa lies at approximately 45° to the mid-line plane, the right heart is as much in front of left heart as it is to its right. The great size of the right lung as compared with the left at this horizontal level is a very obvious feature of the section. Magnification, × 3¾.

The fact that the plane of the septa assumes an obliquity that is between 41° and 45° to the median plane causes the right heart in older fœtuses and in post-partum hearts to be almost, if not as much, in front of the left heart as it does to its right side. This is obviously a feature of cardiac anatomy that is of fundamental significance to both the clinician and the anatomist.

Another relevant fact in the rotation of the heart would appear to be that like all other growth processes, it is in complete harmony with the growth of the surrounding structures and the organism as a whole. It is very noticeable in the study of transverse sections of embryos that while the heart rotates to the left, the right lung attains a greater size than the left, and the right lobe of the liver, growing more quickly than the left, reaches a more cranial level.

This brief statement on the development of the oblique lie of the heart within the thorax is primarily to emphasize that the terms "right heart" and "left heart" are appropriate developmentally and also that the change from a symmetrical to an asymmetrical orientation of the heart

occurs relatively early and is harmoniously associated with the asymmetrical growth of adjacent organs.

Material and Method

The early observations on the rotation of the heart were made on a fairly large series of human embryos ranging in size from 8 mm. (5th week) to 25 mm. (8th week); all of these embryos had been cut serially, most of them transversely but some sagitally, and they form part of the embryological collection belonging to this Department. Some of the fœtuses, i.e. when the embryo had gained a length of more than 25 mm. (after the 8th week of development) were also, when specimens did not exceed 40 mm. in length, cut serially, but single sections of the larger fœtuses were taken at appropriate levels of the thorax and did not always represent part of a continuous series. Eleven full-time fœtuses were cut transversely in sections that varied in thickness from 200μ to 25 mm. (1 inch). Some of the sections were prepared by the technique described by Gough and Wentworth (1949) for the sectioning of whole lungs and the decalcification that was necessary was carried out by 4 per cent nitric acid. The thicker sections were made without decalcification after the thorax had been frozen, either by 48 hours in a refrigerator at −15° C. or by freezing in methylated spirit to

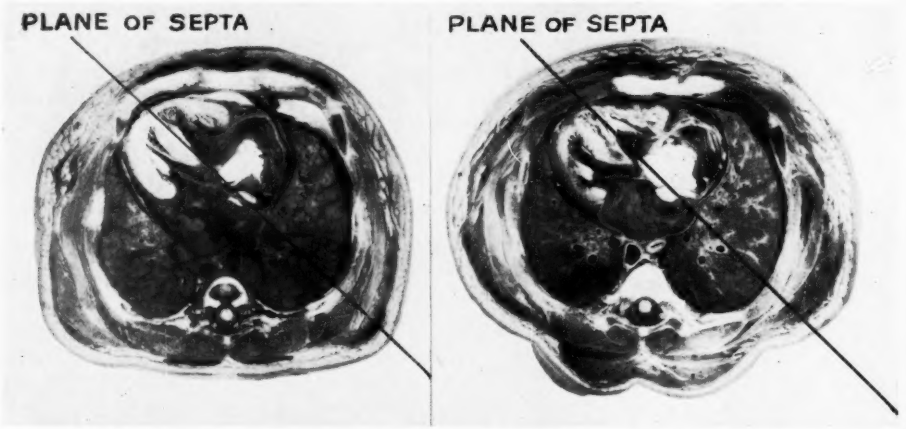


Fig. 3.—Transverse sections through thoraces of two full-time fœtuses. These fœtuses show a difference in the form of their thoraces but this has not caused any apparently great difference in the plane of the heart septa. Magnification, × ½.

which carbon dioxide snow was added. Thereafter these sections were cut on a bandsaw and after re-freezing the surfaces were smoothed by sand-papering. The latter method was employed in the preparation of sections of ten adult thoraces which were cut in transverse, sagittal, or oblique planes. No difficulty is encountered in the preparation of transverse or sagittal sections, except that it is essential that the specimens be frozen throughout if satisfactory sections are to be obtained.

In preparing sections of the right or left hearts, i.e. sections parallel to the septa of the heart, it was always assumed that the atrial and ventricular septa lay at an angle of 45° to the median plane. Photographs of previously prepared transverse sections were, moreover, brought to the approximate scale of the thorax to be sectioned and the distance to the left of the mid-line in front and to the right of the mid-line posteriorly were calculated by reference to these prints before the plane of the "cut" was finally determined. The great variation in the form of thoraces renders it essential for the transverse section that is used to be from a cadaver of the same sex and of approximately that same body type as that on which it is proposed to make the oblique sections.

Similarly, in planning sections of the thorax to show the heart cut transversely to the plane of the septa, it was always assumed that the septa of the heart were at an angle of 45° to the median plane, and again by reference to prints of the correct size, sex, and body type, the distances from the mid-line in front and to the left of the mid-line posteriorly were plotted before the sections were made.

The writer has on each occasion been impressed by the close correlation between the desired and the actual plane of section when the requisite calculations were made beforehand. The procedure, if it is to be successful does, however, require experience in the preparation and cutting of frozen tissues with a mechanical saw and this will be most easily attained by working with someone who is already versed in the technique.

Axis of the Heart and the Plane of the Septa

It is not intended to infer that the plane of the septa as has been described is similar to what is termed the "axis of the heart". The axis is described by Walmsley (1929) as a line which extends from the centre of the base of the heart to its apex and thus passes from behind forwards, downwards, and to the left. The downward inclination of this axis is known to differ considerably

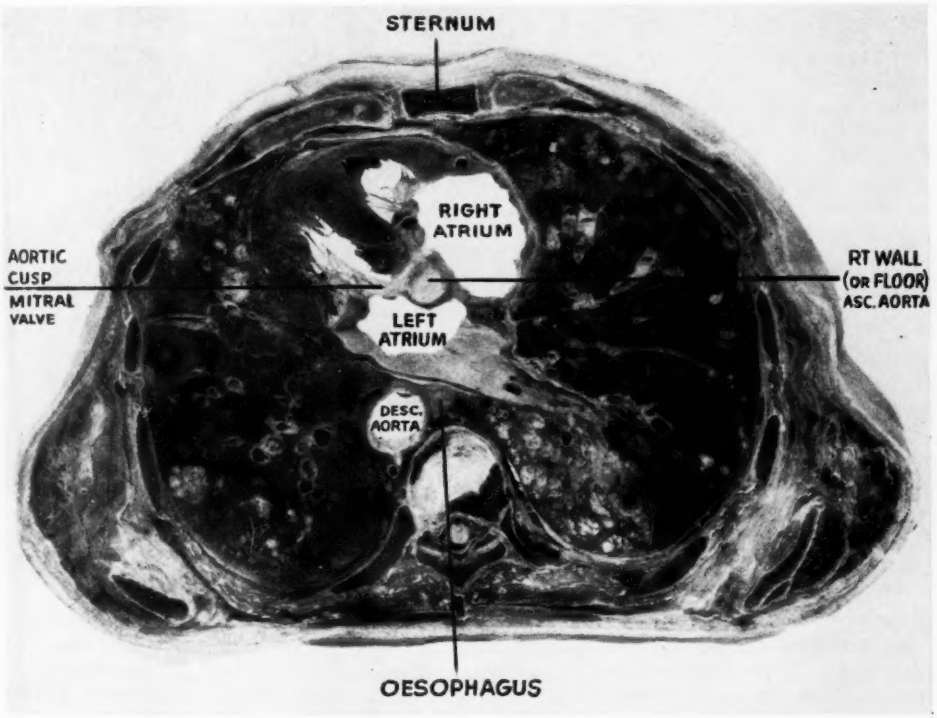


FIG. 4.—Transverse section of adult thorax at the level of the fourth costal cartilages. The section shows all four chambers of the heart, and the obliquity of the septa separating right from left hearts is obvious. The right atrium is dilated, and opening into the left atrium immediately to the left of the atrial septum is the lower right pulmonary vein. A small part of the right wall (or floor) of the ascending aorta is seen immediately adjacent to the aortic cusp of the mitral valve. It may be observed from this section that the blood in passing from atria to ventricles passes forwards and to left through the atrio-ventricular orifices at an angle of approximately 45° to the median plane. The tricuspid valve is fairly closely related to the sternum whereas the mitral valve is much more deeply placed in the thorax.

in living subjects. From the observations that I have been able to make, it would appear that the long axis of the heart is more horizontal in the cadaver than it is in the living (Fig. 6 and 7) and the heart as a whole lies at a higher level. The plane of the septa no doubt also differs considerably in living people but no great difference has been encountered among the eleven full-time fœtuses and the ten adult cadavers sectioned, irrespective of sex or body build. The plane of the septa in all specimens ranged between 41° and 45° to the median plane, but it is appreciated that there may be post-mortem or technique factors that determine this apparent uniformity. It would ill-serve the purpose of this communication to attempt to claim that the form of the heart chambers shown in the photographs of cadaver specimens have their exact counterpart in the living; it is hoped, however, that the photographs here included may form a contribution to a better understanding of living cardiac anatomy.

Fig. 3 is included to show the plane of the septa in two full-time fœtuses that differed fairly strikingly in their thoracic form—a difference that in part is due to a difference in body build and also, as is apparent, to post-mortem artefacts.

A small print of the section shown in Fig. 4 is placed below each of the photographs of the oblique sections, and the plane of each section is indicated on these smaller prints.

Discussion

It is not proposed to enter into a discussion of the many anatomical relationships of importance that have become increasingly apparent during the preparation and examination of these sections, and it would be invidious to discuss the vast literature on this subject. It has perhaps been unfortunate, however, that so many of the classical diagrams of the heart have been made from specimens that had been removed from the body and orientated so that the atria are featured as lying above the ventricles. Current papers, however, more and more tend to consider the heart as it lies *in situ*, e.g. Bedford *et al.* (1957), and this study is based on specimens examined in this way. The atria lie not only behind the ventricles, but to an almost equal extent to their right, and this relationship is determined by the obliquity of the "plane of the septa". Moreover the relationship of the ventricles to each other is erroneously depicted in many standard texts; transverse sections of the ventricles in such figures, for example, show the ventricular septum lying in approximately a sagittal plane with the right ventricle lying almost entirely to the right side of the left ventricle.

The value of the included photographs and observations in the legends is in itself limited. On account of the oblique orientation of the heart in the chest the radiologist not only views it from the front or back but also, as one would expect, resorts to right and left oblique radiographs. It is intended, therefore, that one of the functions of these photographs is to help to clarify certain anatomical features of the heart and great vessels as they are seen in these oblique views. The photographs of specimens cut parallel to the plane of the septa may be compared with radiographs taken in the right anterior oblique position, whereas photographs of specimens cut at right angles to the septa may be correlated with the heart shadow as seen in the left anterior oblique position.

The relationship of the aortic cusp of the mitral valve to parts of the posterior cusps of the aortic valve is extremely close and indeed the bases of these cusps overlap. The proximity of these parts of the two valves is such that it is difficult to understand how from an X-ray film alone it would be possible to differentiate which of the valves is involved in a disease process such as calcification; the movements of a calcified valve on screening may, on the other hand, be of value in reaching a diagnosis.

The rotation of the heart, which as emphasized occurs in the first half of intra-uterine life, causes the left atrium to become indirectly related to the middle thoracic vertebræ thereby forming the posterior surface or base of the heart. The left atrium forms the major *cardiac* relation of the œsophagus but the "left horn" of the right atrium and also a small part of the left ventricle are in contact with it. Fig. 13 shows fairly clearly the close relationship that exists between a part of the left bronchus and the left atrium and is one of the main reasons for including this photograph.

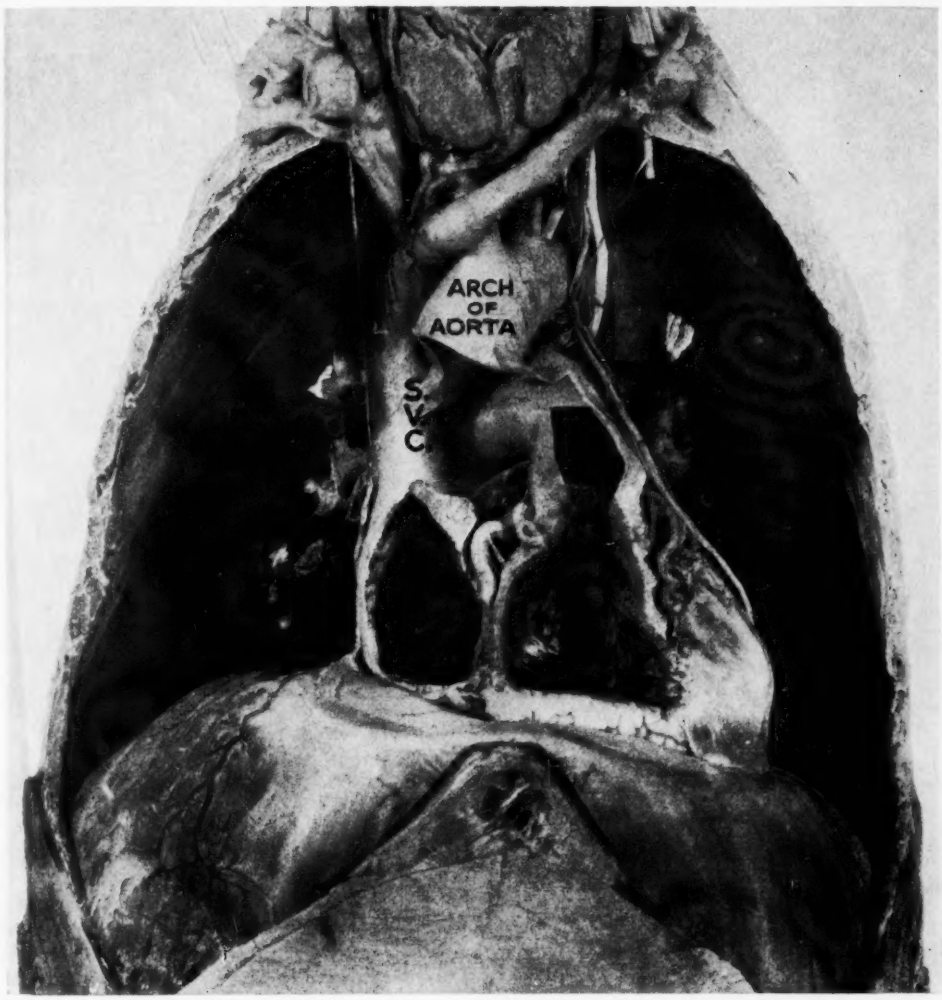
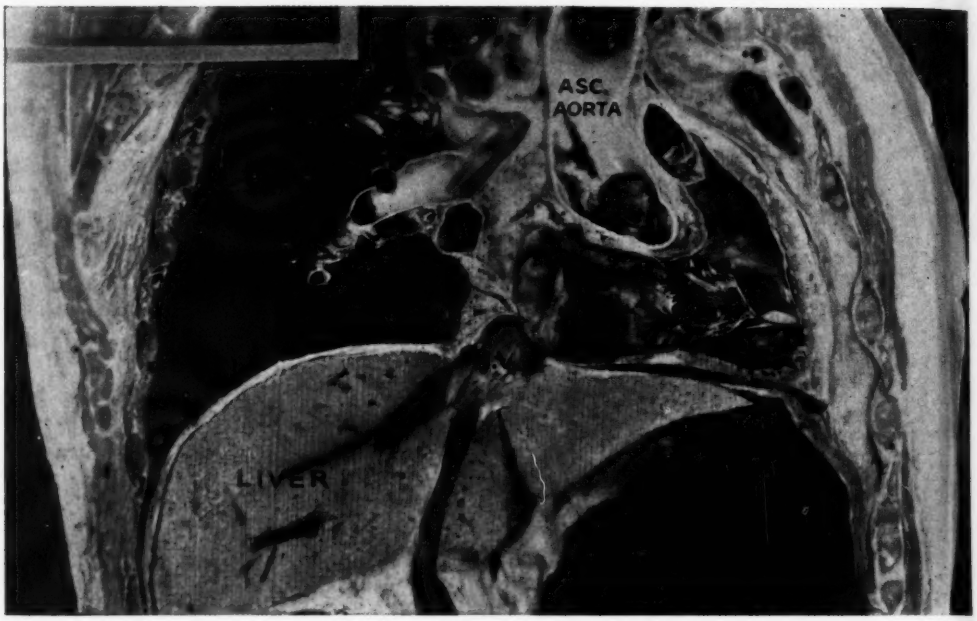
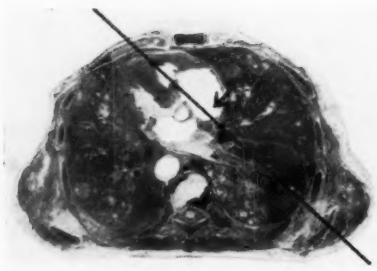


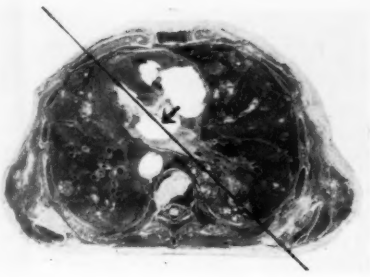
FIG. 5.—Thorax dissected from the front with the heart *in situ*. The anterior walls of the right atrium and ventricle have been removed along with part of the anterior wall of the pulmonary trunk. The right atrium, as is customary in cadavers, is dilated and in it a well-marked valve of the inferior vena cava may be seen. The right border of this atrium is seen to be continuous with the superior vena cava. The greater part of the ascending aorta was removed to expose the right pulmonary artery. The left ventricle, which was not opened, is seen to form the left border of the heart, and when it is followed upwards it is seen to be in line with the left border of the pulmonary trunk. The left auricle frequently embraces the beginning of the pulmonary trunk but it was small in this specimen and is not seen in this view. Above the termination of the pulmonary trunk lies the aortic arch but between the two structures is a gap which is termed the "aortic window".





Continuous line indicates plane of section

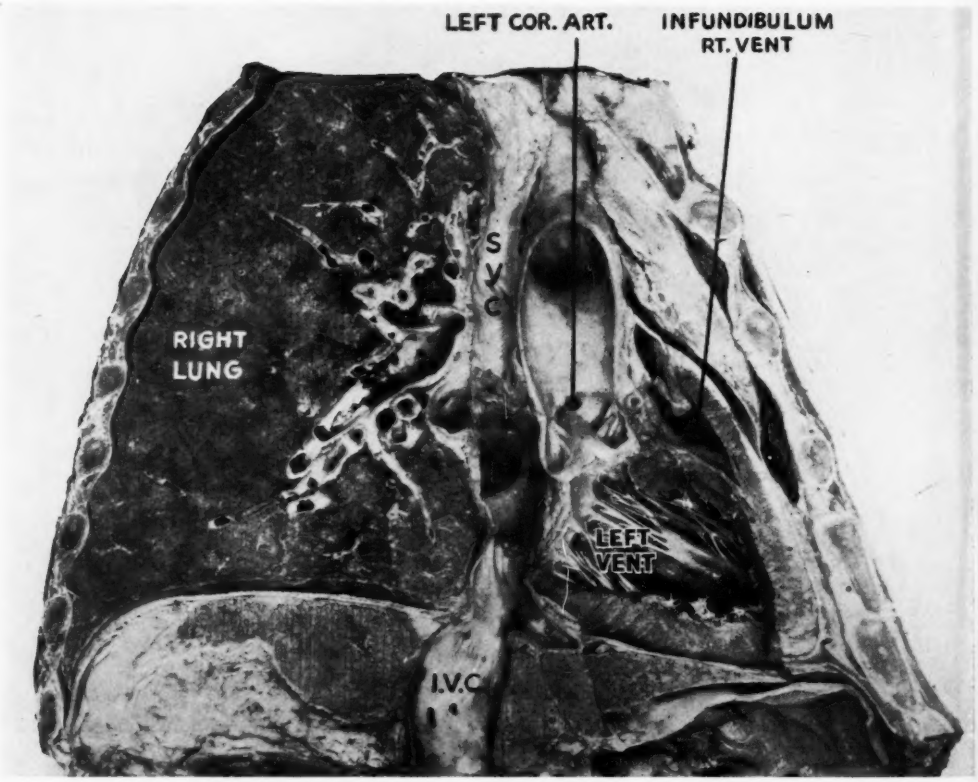
FIG. 6.—Section through right heart viewed from right side and cut in plane shown below. The inferior vena cava is seen passing through the diaphragm obliquely to enter the right atrium, but the superior vena cava is not shown. Immediately in front of the inferior caval opening is the "left horn" of the right atrium (which is occupied by a blood clot) and leads into the coronary sinus; it extends to the left for a short distance below the left atrium and is the only part of the right atrium that is related to the œsophagus. The cusps of the tricuspid valve are prominent and the cavity of the right ventricle has the typical U-shaped form. The infundibulo-ventricular (supra-ventricular) crest is fairly prominent and bounds the infundibulum posteriorly. The cusps of the pulmonary valve are visible and lie at a higher level than those of the aortic valve. The horizontal lie of the diaphragmatic surface of the heart may partly be due to the fixation of the cadaver in a supine position, but it is significant that the orientation of this surface is that which has been encountered in all adult specimens examined. The diaphragmatic surface might equally appropriately be termed the inferior surface.

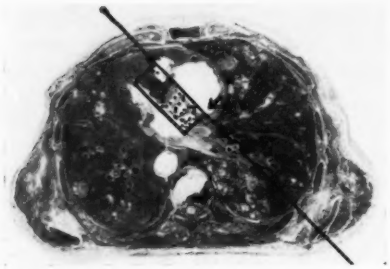


Continuous line indicates plane of section

FIG. 7.—Section through left heart viewed from right side and cut in plane shown below. The left atrium and left ventricle are shown with the mitral valve in between. The "left horn" of the right atrium (filled with blood), which leads into the coronary sinus, lies below the body of the left atrium. A tube was passed along the œsophagus and has been left *in situ*. The œsophagus is here seen to lie behind the left atrium but a small terminal part is related to the "horn of the right atrium". The lower end of the tube emerges from the stomach: this serves to illustrate the close relationship that exists between heart and stomach. The part of the right lung that lay behind the heart was removed to show the posterior part of the thoracic wall: a small part of the left lung was left *in situ* in relation to the sterno-costal surface of the heart.

It will be seen from Fig. 7 that the blood in its passage from left atrium to ventricle passes forwards and to the left at an angle of about 45° to the median plane. As seen in Fig. 6 and 7 there is little, if any, downward inclination of the blood during its course through the atrio-ventricular orifices.





Continuous line indicates plane of section after removal of stippled area

FIG. 8.—Section showing interior of left atrium and left ventricle with the aortic valve and part of ascending aorta *in situ*; the specimen was cut in plane shown below and then the atrial and ventricular septa were removed.

This section and dissection were made to establish the relationship of the cusps of aortic and mitral valves to each other. A large window was cut in the right wall of the ascending aorta, but the entire aortic valve was left intact. The aortic cusps are attached very obliquely so that their upper surfaces are directed almost as much to the right as they are upwards. The aortic cusp of the mitral valve is much larger than the postero-lateral one. The base of the aortic cusp of the mitral valve extends upwards to the attachments of the adjacent parts of the posterior cusps of the aortic valve.

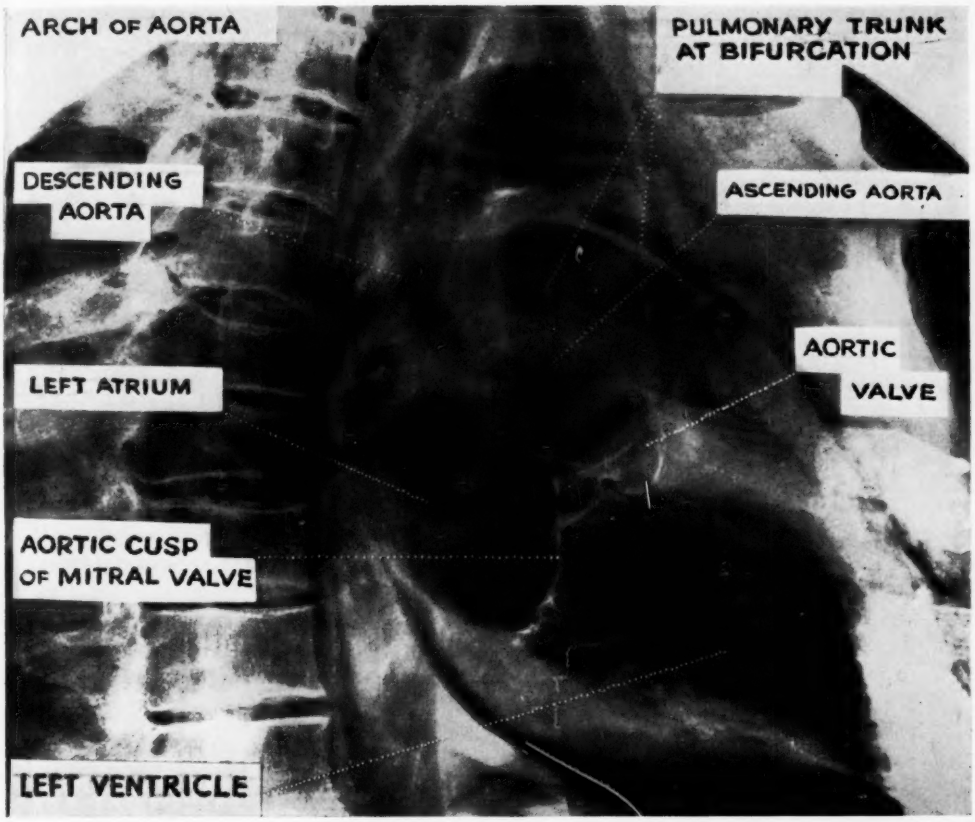
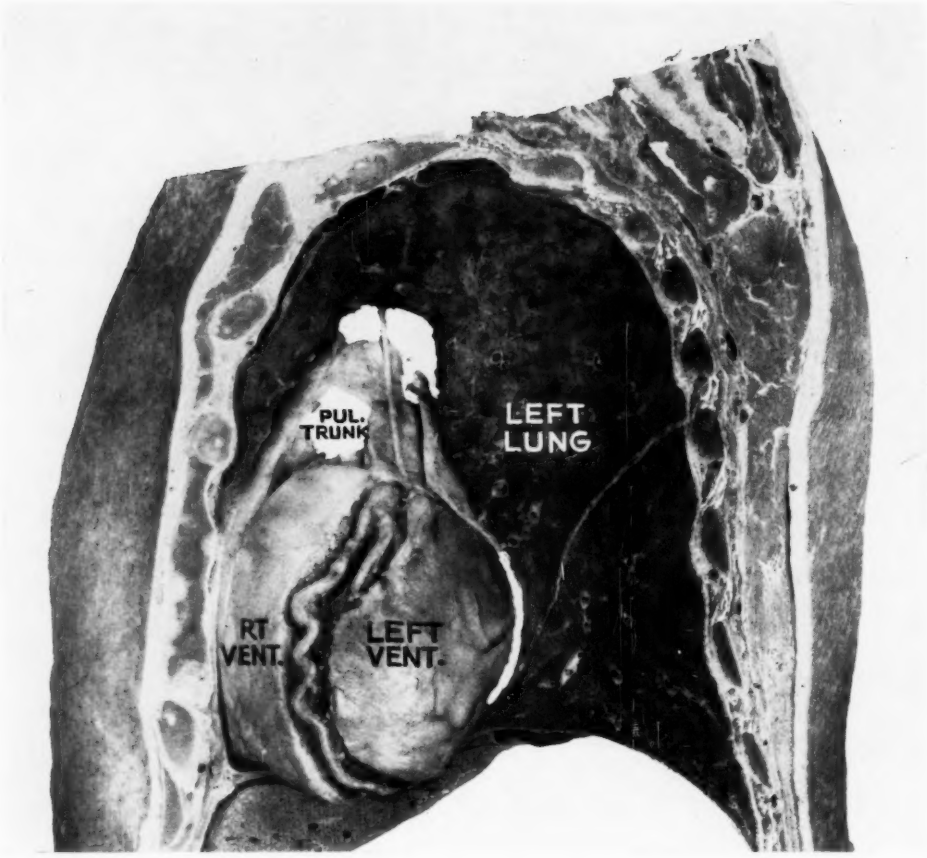
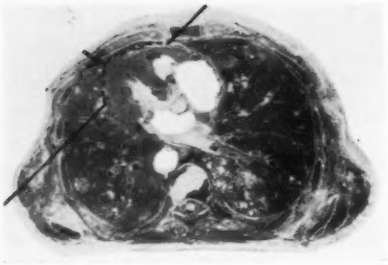


FIG. 9.—The bases of the cusps of the mitral and aortic valves of specimen shown in Fig. 8 were coated with a paste of barium sulphate. There were, moreover, a few calcareous nodules in the cusps of the aortic valve. The specimen was X-rayed and this figure is a print from the untouched radiograph. The close relationship of the upper part of the aortic cusp of the mitral valve to the cusps of the aortic valve is a striking feature and it would appear to make difficult in an X-ray film the differential diagnosis between calcification of the posterior aortic cusps and the aortic cusp of the mitral valve. This radiograph is reproduced at approximately the same magnification as Fig. 8.

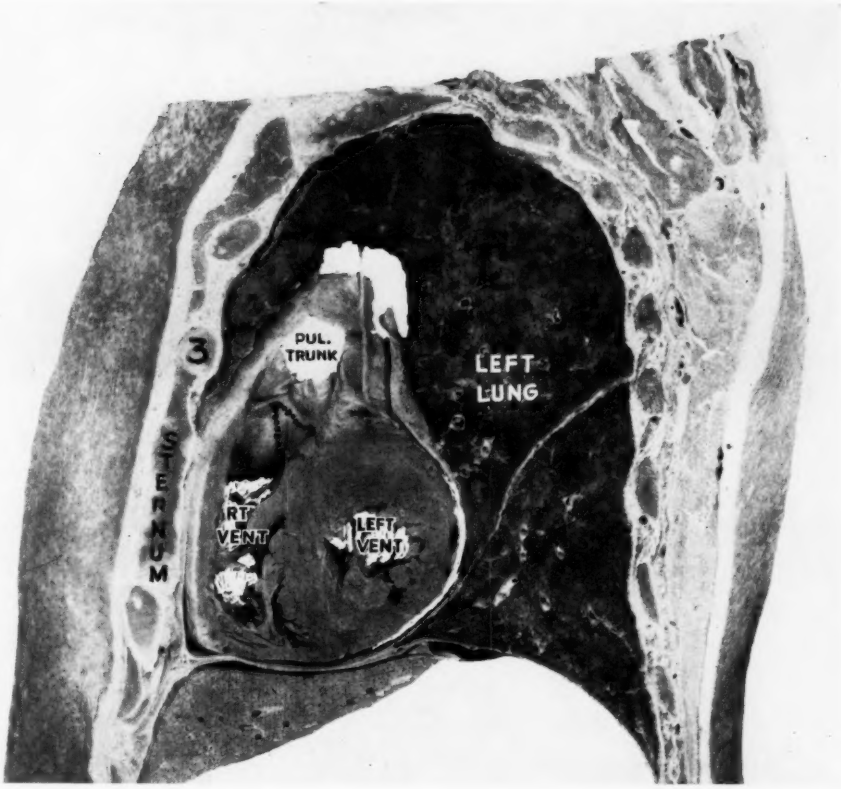


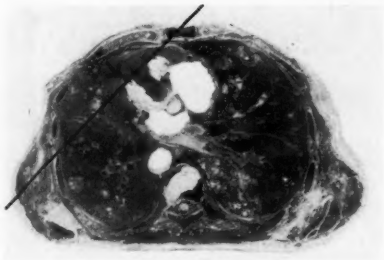


Continuous and interrupted lines indicate plane of section

FIG. 10.—This is one of a series (Fig. 10 to 13, inclusive) in which the heart is viewed along the long axis of the septa. In each of these specimens the heart is viewed from the front and left sides, and together they are equivalent to the view of the heart and great vessels as seen in the left anterior oblique position.

In this specimen the apical part of the heart was removed in the section of the thorax and then replaced before the photograph was taken. The interventricular branch of the left coronary artery lies in the corresponding anterior sulcus and the right ventricle lies in front of it and the left ventricle behind it. A window has been cut in the pulmonary trunk and a part of the left lung adjacent to it has been removed: the left phrenic nerve is seen descending in the space created.

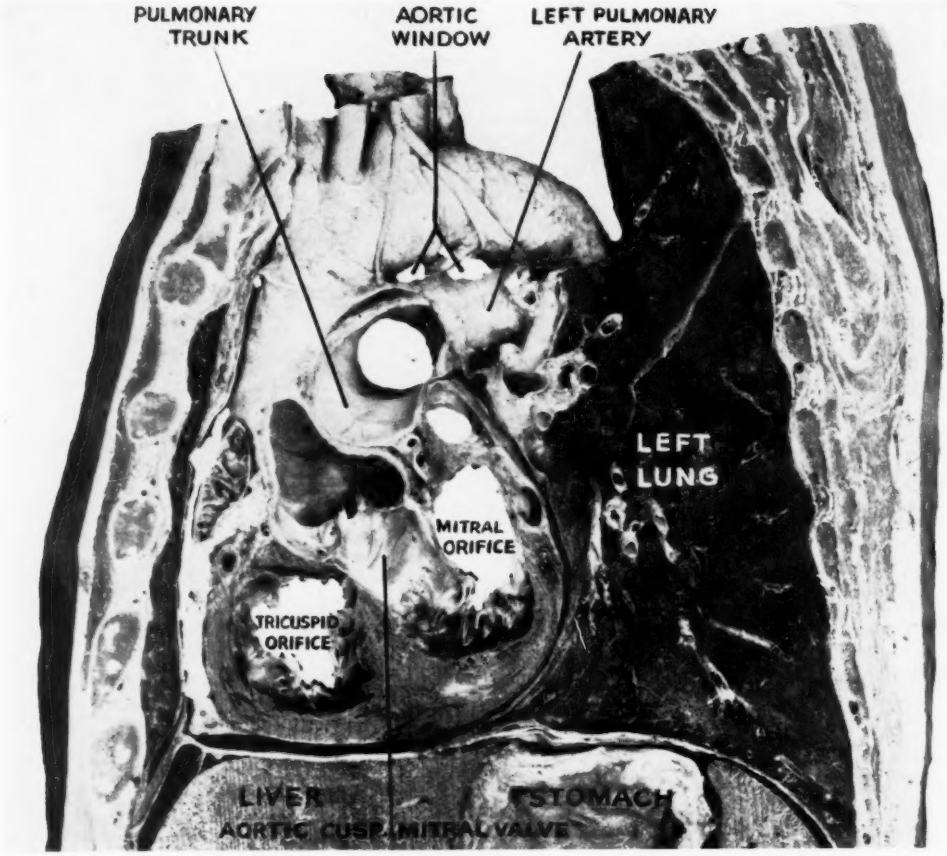


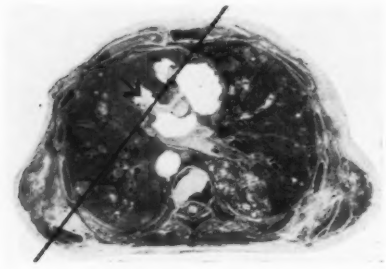


Continuous line indicates plane of section

FIG. 11.—This is the same specimen as that seen in Fig. 10, but the apical part of the heart has been removed as shown below. The heart is cut at right angles to the plane of the ventricular septum and the right ventricle thus lies directly in front of the left; the walls of these chambers have their characteristic form. The window in the pulmonary trunk allows two cusps of the pulmonary valve to be seen, and below this is the infundibulum which constitutes the outflow tract of the right ventricle. The pulmonary cusps lie at the level of the third left costal cartilage (3) at its junction with the sternum and the close relation of the outflow tract of the right ventricle with the sternum just below this level is evident.

On the other side of this section, parts of the anterior and left posterior cusps of the aortic valve were attached and pins were passed through to indicate the relationship of their attachment to the infundibulum. These attachments have been "dotted in" and the part of the anterior cusp is seen as a vertical row of dots with the left posterior cusp attachment extending backwards from its upper end. The aortic valve is very obliquely placed and lies at a lower level than the pulmonary valve.

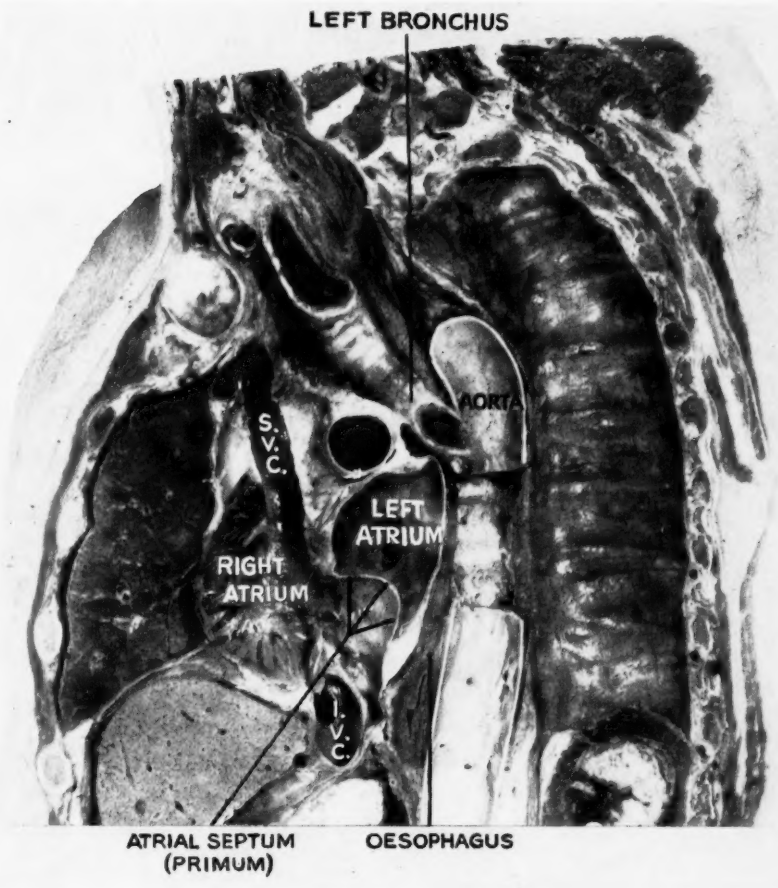


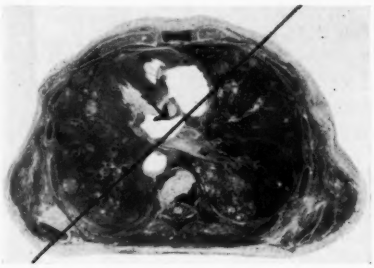


Continuous line indicates plane of section

FIG. 12.—This section is at right angles to the septa of the heart and passes through both atrio-ventricular valves (see small figure below) and also the aortic valve. The close relationship between the large aortic cusp of the mitral valve and the cusps of the aortic valve is evident. A part of the right lung is seen in front of the heart but the left lung lies behind it. Between the left pulmonary artery and the under-surface of the arch of the aorta there is the potential space, termed the aortic window, in which the ligamentum arteriosum is seen to lie.

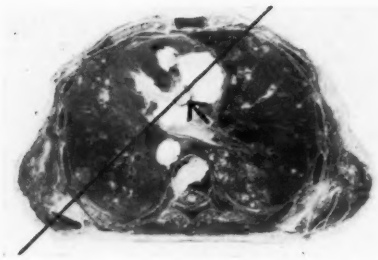
The ventricular surface of the aortic cusp (which is shown) is smooth and this is the structure that forms the posterior wall of the aortic vestibule. The course of the blood from left atrium to aorta is sinuous as may be appreciated by a study of this photograph.





Continuous line indicates plane of section

FIG. 13.—This section is at right angles to the atrial septum and passes through both right and left atria in the plane shown below. The septum primum, which forms the floor of the fossa ovalis, has its customary thinness, whereas the septum secundum, which lies above it, is thick. Both the superior and inferior venæ cavæ are seen opening into the right atrium. The œsophagus may be distinguished passing down behind the left atrium but at its lower end it comes into relationship with the right atrium. The right pulmonary artery lies directly above the left atrium and behind it is the left bronchus. From this photograph it would appear that the contact of left bronchus with left atrium was over only a very short distance, but this is not so, as at least 12 mm. (0·5 inch) of the posterior wall of the left atrium was removed to expose the œsophagus and a corresponding part of the left bronchus was likewise resected.



Continuous line indicates plane of section

FIG. 14.—This section is of a series different from the four immediately preceding. Although it is sectioned in the same plane, i.e. at right angles to the heart septa, it is viewed from the right and behind so that the photograph has been taken looking from the atria towards the tricuspid and mitral orifices (see small figure below).

The cusps of the atrio-ventricular valve project forwards and to the left into the corresponding ventricle. The close relationship of the cusps of the aortic valve to the aortic cusp of the mitral valve is again evident. Glass rods have been inserted into the left common carotid and left subclavian arteries and are very obvious, and rods in the coronary arteries may also be seen.

It is obvious from this section that the aortic cusp of the mitral valve might equally well be termed the "antero-medial" cusp and this would be in keeping with the use of the term "postero-lateral" for the opposing cusp of that valve.

FIG. 15.—This X-ray is of the same specimen shown in Fig. 14 and is of the same magnification. One pin was inserted as nearly as possible into the attachment of part of the right posterior cusp of the aortic valve and another was inserted along the line of attachment of the upper part of the aortic cusp of the mitral valve. The specimen was then radiographed and the close relationship of the pins is very evident. The thick wall of the left ventricle as seen here is not visible in Fig. 14, but many other features may be correlated with the photograph.

This communication is primarily a plea that gross cardiac anatomy should always be considered with the heart lying *in situ*. This, it is believed, is the only means that will allow the surfaces, the cusps of the valves, and other structures to be designated by names that are precisely appropriate to them, and what is more important, give an understanding of the relative position of the heart chambers, valves, and great vessels to one another. When the heart has been removed post-mortem, it shows changes in its form and is easily distorted so that it is difficult to reconstitute the shape that it had in the body, either before or after death.

Summary

The human heart in young embryos is approximately symmetrical with the atrial and ventricular septa almost in the median plane. A rotation occurs which carries the anterior interventricular sulcus to the left and after about 4½ months of intra-uterine life the heart has assumed its adult position with the atrial and ventricular septa at an angle of about 45° to the median plane.

Sections were prepared of the adult thorax by cutting with a band-saw after the specimen had been frozen. Sections were made parallel to the septa so as to pass through both the right and left sides of the heart: these may be of value in interpreting X-ray films taken in the right anterior oblique position. So, too, were sections made that cut the heart at right angles to the plane of the septa, and these may be considered with films taken in the left anterior oblique position.

Photographs of representative specimens constitute the major part of this contribution to the anatomy of the adult heart. Two of the photographs are supplemented by radiographs in which the aortic cusp of the mitral valve and parts of the posterior cusps of the aortic valve are indicated by radio-opaque substances.

The legends to the photographs make reference to some of the principal relationships. No review is made of the literature nor is it discussed, but a short discussion of the specimens is included.

A work of this nature requires the cooperation of several people. Foremost I should like to acknowledge my deep indebtedness to Professor I. G. W. Hill, not only for his very considerable help and guidance, but also for giving to me the initial stimulus to prepare the series of sections from which the selected photographs have been made. I also would like to record my thanks to Dr. J. W. Smith and J. Mutch who both assisted me in planning the plane of the sections and also in cutting the thoraces, and also to Mr. P. D. Bewsher for the dissection of the specimen shown in Fig. 5. The photography is the work of the senior technician of the Department, Mr. James Brown, and without his skill and patience this contribution could not have been made. I am indebted to Dr. W. F. Mair for the two radiographs.

References

Baxter, J. S. (1953). *Frazer's Manual of Embryology*. 3rd ed., Baillière, Tindall & Cox, London.
Bedford, D. E., Sellors, T. H., Somerville, W., Belcher, J. R., and Besterman, E. M. M. (1957). *Lancet*, **1**, 1255.
Gough, J., and Wentworth, J. E. (1949). *J. Roy. Microscop. Soc.*, **69**, 231.
Walmsley, T. (1929). *The Heart. Quain's Elements of Anatomy*. 11th ed., Vol. IV, Pt. III., Longmans, Green, London.

SELECTIVE CINE-ANGIOCARDIOGRAPHY WITH IMAGE INTENSIFICATION

BY

HAMISH WATSON, C. PICKARD, K. G. LOWE, AND IAN HILL

From the Departments of Medicine and Radiology, University of St. Andrews

Received February 12, 1958

There has been steady progress in angiocardiographic technique since Castellanos *et al.* (1937) showed that satisfactory opacification of the heart chambers was possible in children, and Robb and Steinberg (1938) confirmed that equally successful results could be obtained in adults. Though the earliest attempts to visualize the interior of the heart had been unsuccessful, it is interesting to note that in these the contrast medium had been introduced directly into the heart (Forssmann, 1931; Pérez Ara, 1931; and Moniz *et al.*, 1931). Most of the subsequent work was done using intravenous injection, and it was not until 1946 that a reliable method of direct intracardiac angiocardiography was described by Chavez *et al.* (1947). Since then much thought has been given to methods for rapid and safe intracardiac injection (Jönsson *et al.*, 1949; Dorbecker *et al.*, 1954; Gidlund, 1956; and Rodríguez-Alvarez and de Rodríguez, 1957) and, though they are not yet perfect, many of their earlier dangers and disadvantages have been overcome.

The introduction of image intensification by Teves and Feddema (1953 and 1955) started a new era in diagnostic radiology and the combination of the intensifier with a cine camera has provided an

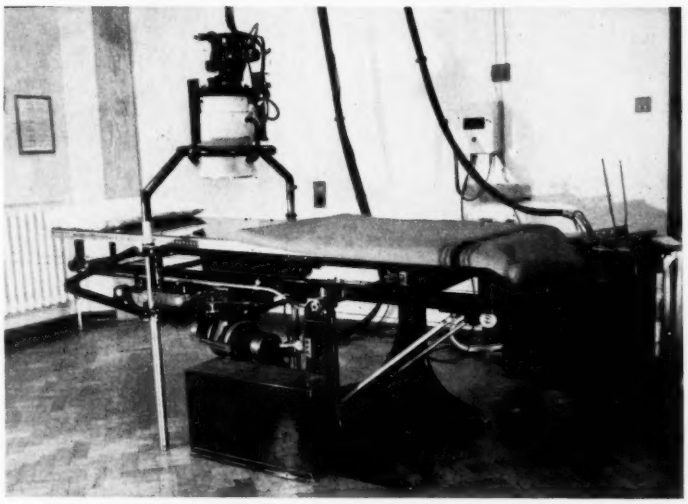


FIG. 1.—This shows the general arrangement of the tilting table with a mobile top, and the radiological apparatus.

instrument that is particularly well suited to the field of angiocardiography (Lind and Wegelius, 1955; Astley, 1955 and 1956; and Stauffer *et al.*, 1955). When it is used with a good technique of selective injection, the films made can be studied either in motion, at normal or slow speeds, or projected as serial stills, and this results not only in more accurate diagnosis but allows detailed study of the actual intracardiac circulation. In addition the comparatively small radiation rates used (Feddema, 1953; and Lind *et al.*, 1955) mean much greater safety for both patients and staff—a factor now rightly considered of the utmost importance.

Equipment and Methods

The installation is illustrated in Fig. 1 and some results in Fig. 2, 3, and 4. It consists of a tilting table with a mobile top. The undercouch tube is a Super Dynamax with a 1 mm. focal spot, and the focus is 24 inches (60 cm.) from the skin surface. The operator controls the beam delineation by a double diaphragm which affords full protection. Power is supplied to the tube from a Watson cine-generator and, as the H.T. cables are long, no further stabilization is required with low continuous tube currents. The explorator has been replaced by a Philips 5-inch (12·5 cm.) intensifier which can be used with a fluorescent tunnel, a direct lens system, or a 35-mm. cine camera. Standard fluorescent screen examination is also possible over a 12-inch (30-cm.) square area, and spot films can be taken if required.

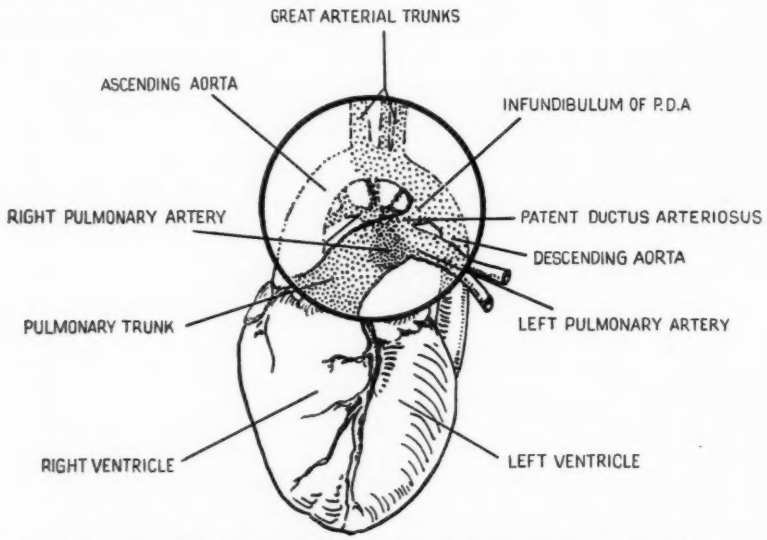


Fig. 2.—The relationship of the intensifier field to the heart and great vessels (left anterior oblique view).

Fig. 3 and 4 illustrate two sets of twelve consecutive pictures taken at 50 frames a second, from a selective cine-angiocardiogram done on an 8-year-old girl, who presented as a case of Eisenmenger's syndrome (Wood, 1952). The investigation was carried out after clinical examination and cardiac catheterization had failed to differentiate between a ventricular septal defect and patency of the ductus arteriosus.

Fig. 3.—In pictures 1–5 the initial opacification of the patent ductus arteriosus is seen developing and its infundibulum (Steinberg *et al.*, 1943; Jönsson and Saltzman, 1952) is clearly defined. The contrast medium outlines the descending aorta (6 and 7), and thereafter retrograde opacification of the first part of the descending aorta and the aortic arch takes place (8–12). See page 461, opposite.

Fig. 4.—The first picture, at the end of diastole, shows that the innominate artery and the distal half of the aortic arch are opacified. In the second picture systole begins and the non-opaque blood from the left ventricle "washes out" the contrast medium down to the level of ductal entry (2–7); with diastole the retrograde opacification begins again and progresses upwards (8–12). See page 463.

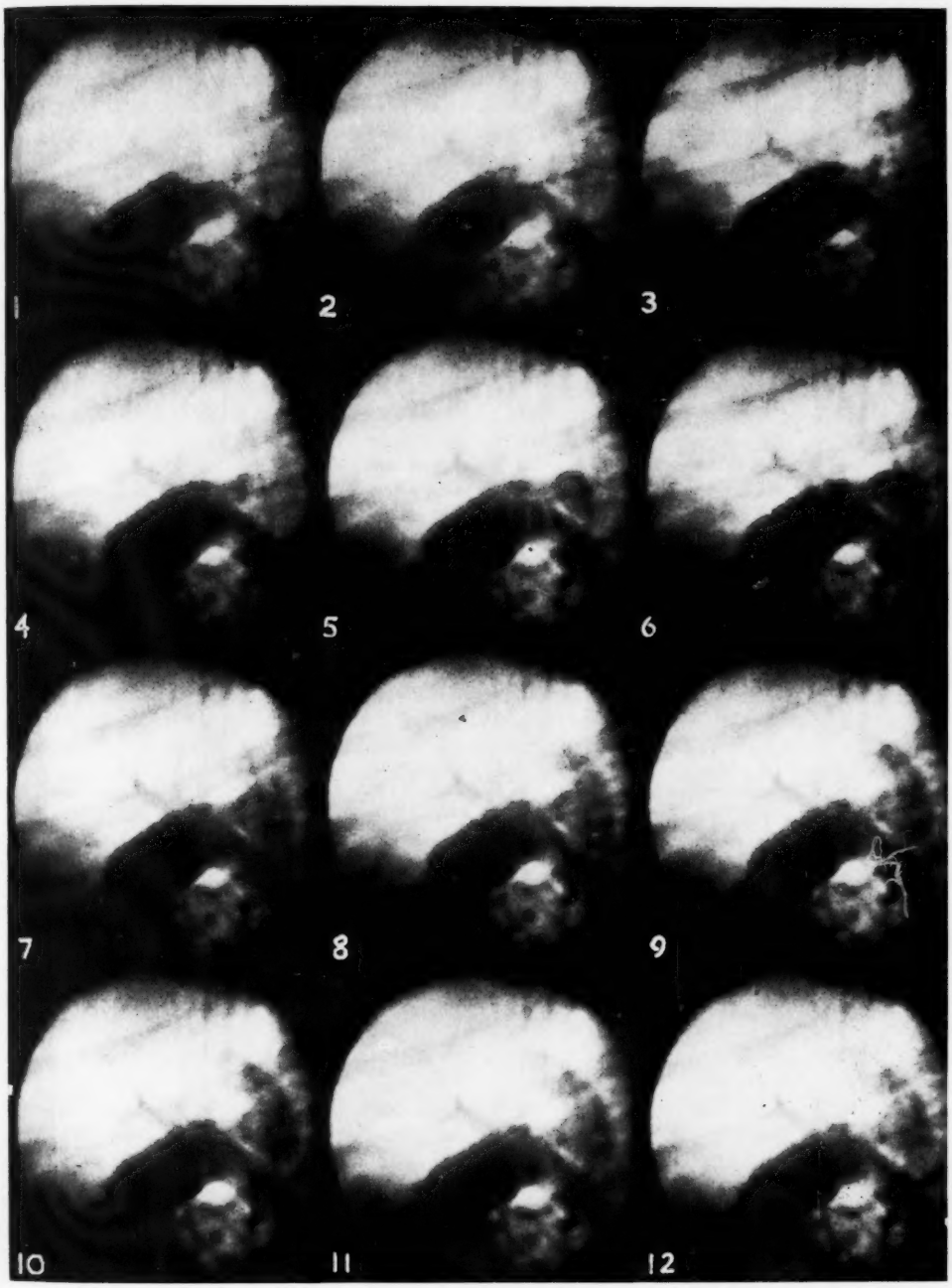


FIG. 3.

The control of the exposure for cine-radiography is now standard. A micro-voltmeter is in circuit and arbitrary figures have been established that correlate the size and thickness of patient, the speed of the camera, and the radiographic output from the tube. This system has been satisfactory for all the speeds so far used. At lower speeds radiographic factors of the order of 65 KV and 1 MA are utilized, but at higher speeds, 100 KV and 5 MA are required. A stationary grid has been found an advantage and the filtration of the tube varies from 0·5 to 3 mm. depending upon the KV applied. As the period during which cine-radiography is in operation does not usually exceed 12 seconds, it has not been found necessary to involve complicated switching devices. During the preparation of the installation, much detailed work was carried out on the photographic aspects of this technique, and after experimenting with a variety of methods, HPX or Scopix G.35-mm. film, processed under standard conditions with standard solutions, has been found satisfactory for most cases, and the master film is available for preliminary examination within a few hours.

There is no doubt that at present the main disadvantage of image intensification is the small size of the screen, and like others we have found that this rather limits its usefulness. But as the investigation of congenital heart disease is largely confined to children, the 5-inch (12·5-cm.) field is less restrictive than would at first sight be imagined. It does, however, mean that, as we can at present only film in one plane, the greatest care must be taken with the positioning of the patient if the maximum information is to be obtained. In our preliminary studies we have used variations of the left anterior oblique view, depending on the nature of the lesions present, and have found that this gives good visualization of the heart chambers and great vessels. In infants and young children, where the size of the screen is no problem, this represents a good compromise in the absence of the usual biplane photography and gives satisfactory results. When it is not possible to get the whole heart on the screen, the field is centred on the particular area that will give most help in the diagnosis and future surgical treatment.

If in addition to diagnosis and pre-surgical evaluation, the intracardiac circulation is to be studied, it is essential that the injection be truly selective. To make certain of this is by no means easy because the action of the heart, the rotation of the patient into the desired position, and the force of the injection itself tend to produce movement of the catheter tip, and may cause it either to change its position within the cavity or to move out of it altogether. If, for example, the right ventricular outflow tract and pulmonary valve are to be studied, the contrast medium is injected into the lower part of the right ventricle with the intention that ventricular contraction will push it up into the infundibulum. If the catheter moves up or points up into the infundibulum during the injection, the result is a pulmonary arteriogram and neither the filling mechanism nor the anatomy of the outflow tract will be defined. On the other hand should the force of the injection push the tip of the catheter back into the right atrium, only the initial opacification takes place in the ventricle, and very quickly the unwanted right atrial shadow obscures the detail of the outflow tract and pulmonary valve.

The size of the catheter used varies and is not necessarily the largest one possible. When selecting it, the size of the heart as well as the size and age of the patient have to be considered carefully and in the light of previous experience, if good pictures are to be obtained. For babies a No.5 catheter is used and the injection given as rapidly as possible, but with larger sizes in older children the force of the injection is varied to suit the problem that is being investigated, and the tip of the catheter is shaped and fixed to match the size of the heart and the site of injection in each case. A leg vein is used for the catheterization for two reasons: firstly because in babies and very small children it is easier, and secondly because we have found that if an arm vein is used and films are taken in oblique positions, the catheter may obscure structures to be visualized. When the catheter is in the desired position, it must be securely anchored to the skin of the limb if the force of the injection is not to cause it to change position, and the use of catheters with lateral holes near the tip does much to reduce recoil during the injection.

Not only the choice of the site of the injection, but also the means used to ensure that the contrast substance is in fact delivered there, have an important effect on the value of what is eventually

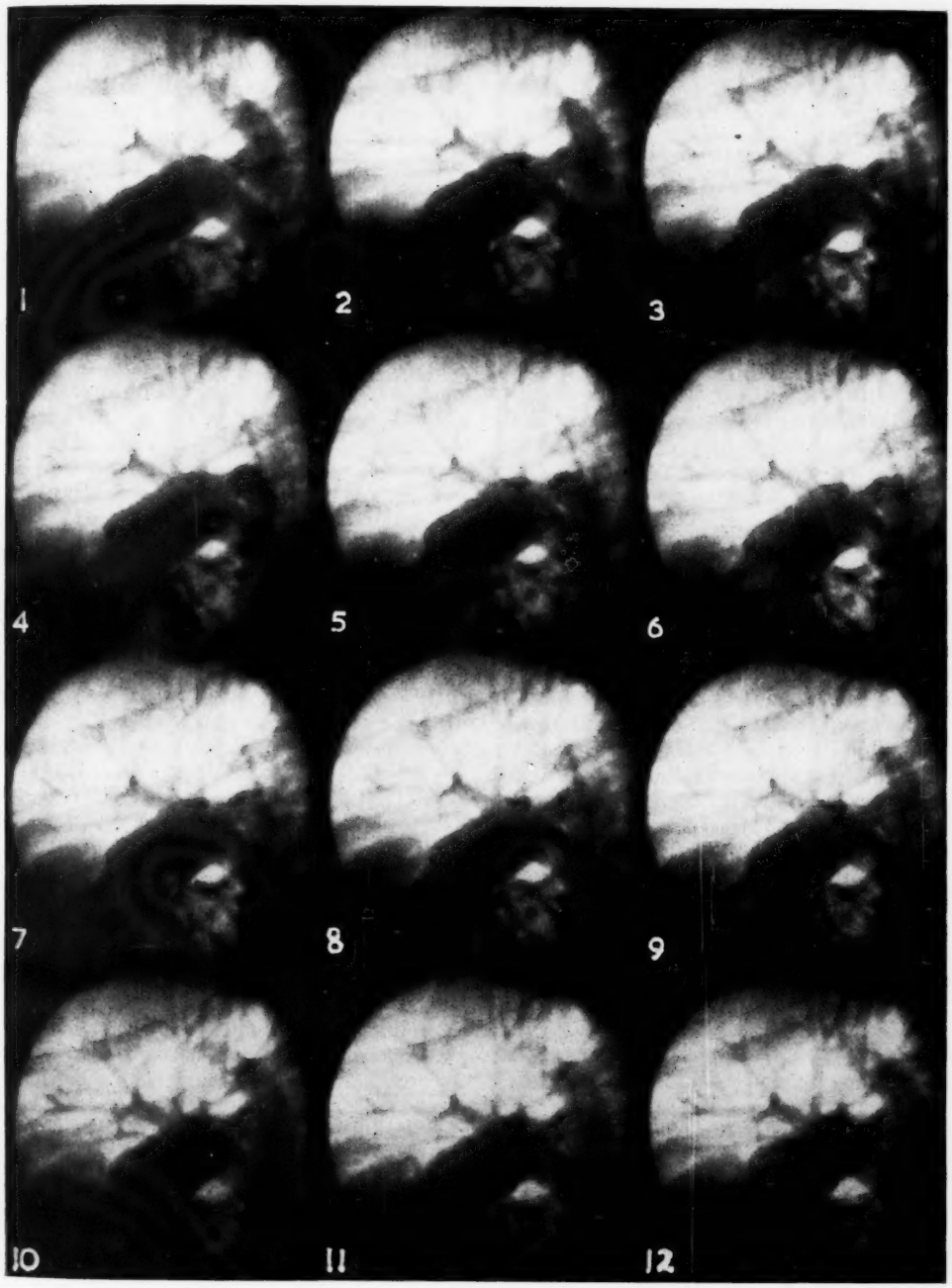


FIG. 4.

seen on the cinematograph screen. As the field to be photographed can be seen through a lens or tunnel in full lighting, it is a simple matter to check the position of the patient and the site of the catheter tip right up to the moment of injection.

When angiocardiograms are studied in motion, opacification is much more obvious than it is on still pictures, and can be seen where, on stills, there would be some doubt as to whether or not faint delineation is present. With our usual technique ultra-rapid injection is not required, and the aim is to produce adequate opacification over several cardiac cycles. However, since at rapid film speeds faint delineation is fairly obvious, we have been trying two or more smaller injections in different planes, though still keeping the total dose of contrast medium within normal limits. For this it is essential that the small volume of contrast substance enters the heart as a bolus, and the object is to be sure of catching at least one complete cardiac cycle showing the initial opacification. Though there are obvious drawbacks we hope that some such modification in technique will prove satisfactory for selected cases and that in this way still more information will be obtained.

The problem of correlating angiocardiographic films with events in the cardiac cycle is one that has in the past received surprisingly little attention, perhaps because it is not vitally important in many cases with slower film speeds. With cine-photography accurate timing is of first importance if the intracardiac circulation is to be studied in detail. A simple device that produces automatic exposure marking on a synchronous electrocardiogram (Lind *et al.*, 1954) has been successfully modified for this purpose and the time relationship of single pictures can be determined. If in addition the duration of the injection is shown on the recording paper, an exact correlation between electrocardiogram, X-ray picture, and injection of contrast medium is produced. This time relationship can be further checked, if by means of a simple circuit a given electrocardiographic signal, say the top of the R wave, produces a light spot on the film.

One of the major difficulties encountered has been in the presentation of the results for analysis. This has been tackled in various ways (Campeti *et al.*, 1955; Greenwood, 1956) but the general principle that we have now adopted is to have the master film, approximately 80–100 ft., processed, examined for possible faults, and then sent away for professional copying. As it is difficult to project 35-mm. film in this country because of the existing safety regulations, the prints are reduced to 16 mm. and there is little or no loss of quality or contrast in the process. We have found the definition on the 35-mm. film quite satisfactory, and because we think analysis is easier when the contrast medium appears black, a positive 16-mm. film is made from the original 35-mm. negative. Detailed examination is not carried out until the prints are available, and though this means a certain amount of delay, the master film is protected from wear and tear and filed for future reference.

It takes time to adapt to this new method of presentation, and the eye accustomed to conventional angiocardiography finds that the speed of events is a little confusing. When running the film through as serial stills it has to be constantly borne in mind that the time interval between pictures is very small: otherwise, a false impression of persistent opacification in this or that chamber or vessel will be created. We are convinced that slow motion projection is essential for detailed studies, but at present this is not easy to achieve. The maximum camera speed commonly in use is about 50 frames a second, and is too slow for a genuine slow motion effect. This can, however, be simulated by using skip-frame optical projection in printing, which though very effective is also very expensive. The aim must therefore be to increase the camera speeds so that slow motion projection is possible, and with this in mind we have now produced satisfactory films with more than 70 frames a second. It has been suggested that image persistence may arise at faster speeds, and though this may well be a problem in the future, we have not been troubled by it so far.

Discussion

Angiocardiography, while presenting a factual record for analysis, is very much subject to the personal factor in interpretation. Nowhere perhaps is this more true than in the study of the opacification of the right ventricular outflow tract in pulmonary stenosis: here the greatest difficulty

may be experienced in distinguishing between the normal infundibulum in varying stages of contraction and infundibular stenosis. The healthy outflow tract is funnel-shaped and of much greater diameter than the adjacent pulmonary trunk, but in our experience this fully dilated phase is a very momentary event, and in a child with a fairly rapid heart rate the chances of catching it on single films are very small. The main problem facing those interested in angiocardiography has therefore been to get increased film speeds without raising the already high radiation rates. The use of image intensification and cine-photography not only helps to solve this problem, but makes it possible to take five times as many pictures per second as the fastest conventional machines with a considerable reduction in the dose of X-rays received by the patient. Though the methods of its application are still in a developmental stage it is already obvious that this is an advance in diagnostic technique. It is, for example, always possible at these film speeds to see the right ventricular outflow tract fully dilated and to decide whether narrowing is present or not, and this kind of detailed study of the intracardiac circulation in patients with congenital heart disease will lead to a much clearer understanding of the abnormal mechanisms involved (Fig. 2, 3, and 4).

Summary

Selective cine-angiocardiography using a Philips image intensifier is described, and the technical problems of production and presentation of the films for analysis are discussed. The future possibilities of this method in the investigation of congenital heart disease are emphasized.

References

Astley, R. (1955). *Brit. J. Radiol.*, **28**, 221.
—— (1956). *Brit. J. Radiol.*, **29**, 556.
Campeti, F., Gramiak, R., Watson, J. S., Ramsey, G. H., and Weinberg, S. (1955). *Circulation*, **12**, 199.
Castellanos, A., Pereira, R., and Garcia, A. (1937). *Arch. Soc. estudios clin. Habaña*, **31**, 523.
Chavez, I., Dorbecker, N., and Celis, A. (1947). *Amer. Heart J.*, **33**, 560.
Dorbecker, N., Rodríguez-Alvarez, A., and Volnie, B. (1954). *II Congreso de Cardiologiá SIBIC-Acapulco, Mexico.*
Feddema, J. (1953). Annual Congress, Brit. Institute of Radiology.
—— (1955). *Brit. J. Radiol.*, **28**, 217.
Forssmann, W. (1931). *Münch. med. Wchnschr.*, **78**, 489.
Gidlund, A. (1956). *Acta Radiol., Supplement*, 130.
Greenwood, F. G. (1956). *Brit. J. Radiol.*, **29**, 544.
Jönsson, G., Brodén, B., and Karnell, J. (1949). *Acta Radiol.*, **32**, 486.
——, and Saltzman, G. F. (1952). *Acta Radiol.*, **37**, 445.
Lind, J., Wegelius, C., and Lichtenstein, H. (1954). *Circulation*, **10**, 195.
——, —— (1955). *Nord. Med.*, **22**, 914.
——, ——, and Boesen, I. (1955). Henry Ford Symposium on Cardiovascular Surgery, Detroit.
Moniz, E., de Carvalho, L., and Lima, A. (1931). *Presse méd.*, **39**, 996.
Pérez Ara, A. (1931). *Rev. méd. circ. Habaña*, **36**, 7.
Robb, G. P., and Steinberg, I. (1938). *J. clin. Invest.*, **17**, 507.
Rodríguez-Alvarez, A., and de Rodríguez, G. M. (1957). *Amer. Heart J.*, **53**, 481.
Stauffer, H. M., Morton, J., Oppenheimer, M. J., Stewart, G. H., and Blackstone, A. W. (1955). *Radiology*, **65**, 784.
Steinberg, M. F., Grishman, A., and Sussman, M. L. (1943). *Amer. J. Roentgenol.*, **50**, 306.
Teves, M. C. (1953). Annual Congress, British Institute of Radiology.
—— (1955). *Brit. J. Radiol.*, **28**, 216.
Wood, P. (1952). *Brit. med. Bull.*, **8**, 348.

THE CORRELATION BETWEEN VARIOUS ASSESSMENTS OF PULMONARY ARTERIAL PRESSURE IN MITRAL STENOSIS.

BY

J. F. BOYD, S. D. SCOTT PARK, AND GEORGE SMITH

From Departments of Pathology, Radiology, and Surgery, Western Infirmary and University of Glasgow

Received November 11, 1957

In a random sample of 50 patients with mitral stenosis who had undergone mitral commissurotomy, the radiological assessment of the pulmonary vascular status was compared with other methods for assessing this feature. In each case, from the data available, the following were selected. (*a*) The clinical grading. (*b*) The pressure in cm. of saline recorded in the main pulmonary artery; only the mean pressure has been utilized. (*c*) The assessment of the pre-operative radiographs. (*d*) The histology of the tip of the lingular lobe of the left lung, obtained at operation. Each investigator assessed independently the degree of pulmonary vascular change that might be expected in each case from the particular data with which he was most familiar. These results were then correlated with those of the other members of the team.

Results

(1) *Clinical Data.* Among the 50 patients there were 37 women. The sex distribution in the sample, therefore, is the same as that in our larger series and in those of others: namely about three women coming to mitral surgery for every man. The ages of these 50 patients ranged from 16 to 48 years. While the symptoms complained of varied greatly, all patients had breathlessness of various degrees of severity, extending from as short a period as three months to as long as 28 years in duration. In 19 there was paroxysmal dyspnœa. In 26 there was a history of hæmoptysis of various grades of severity. Before operation there had been four episodes of systemic arterial emboli in three patients.

The pre-operative clinical grading of each patient was made according to the criteria used by Baker *et al.*, 1952 and 10 were in grade 2, 34 in grade 3, and 6 in grade 4.

(2) *Pulmonary Arterial Pressures.* The mean pressure was determined by puncturing the main pulmonary artery with a needle connected to a saline manometer immediately the chest was opened at operation and before the left lung was collapsed. Zero point of reference was taken as the root of the main pulmonary artery. The systemic arterial pressure was noted at the same time. In some cases cardiac catheterization had been carried out before operation. In the main there was no gross discrepancy between the mean pulmonary arterial pressure determined at this time and later at the time of operation. It was 20–40 cm. saline in 8 cases, 40–60 cm. in 17, 60–80 cm. in 14, and above 80 cm. in 11.

(3) *Radiological Assessment.* The films available for study consisted in most cases of a P.A. view taken at standard distance with standard technique (Whitaker and Lodge, 1953). The films together with a fluoroscopic examination had mostly been taken within the period of a fortnight before operation, but in one or two there was an interval of a few months during which period the cardiovascular status of the patient might conceivably have altered.

From each film, the following points were studied: overall heart size, size of the individual chambers, the presence of valvular calcification, the size of the aortic knuckle, the pulmonary conus, the main pulmonary artery and branches, the hilar vessels, the state of the perihilar vessels, the occurrence of "amputation" of the pulmonary arterial branches (Steiner and Goodwin, 1953), the general state of the lungs, the occurrence of hæmosiderosis, the presence of old infarcts or of pleurisy, and the presence or absence of horizontal lines. For the assessment of the height of the pulmonary arterial pressure, the following points were considered to be important: (*a*) the heart size (a small heart was rarely associated with a high pulmonary arterial pressure); (*b*) the size of the pulmonary artery; (*c*) the size of the hilar vessels; (*d*) the state of the perihilar vessels; (*e*) the presence of amputation of the pulmonary arteries; and (*f*) the occurrence of horizontal lines.

The size of the pulmonary conus was found to bear no relation to the presence or severity of pulmonary hypertension.

Based on these criteria, the films were graded into four groups: 2 showed no abnormality, 14 mild changes, 22 moderate, and 12 severe changes. An example of the mildest and severest grade is shown in Fig. 1 and 2 respectively.

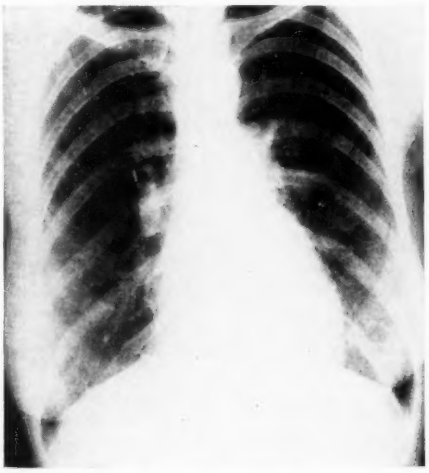


FIG. 1.—Example of minimal radiological changes.

FIG. 2.—Example of gross radiological changes.

(4) *Histological Assessment.* The lingular biopsies were removed with the lung expanded so that distortion would be minimal. The conical piece of tissue measuring roughly 2·5 cm. in length by 2·5 cm. across the base was immersed immediately in 10 per cent formol-saline and later sliced parallel to the base. All the material was processed. Sections were stained by hæmatoxylin and eosin and by Weigert's method for elastica: Masson's trichrome stain and Perl's method for hæmosiderin were used when required.

In each case, five pulmonary arterioles which were cut transversely were measured by a micrometer. The mean diameter of the lumen and the mean wall thickness were thus obtained according to the method originally reported by Kernohan *et al.* (1929). From each case, therefore, an average lumen/wall ratio was obtained and the distribution of this for the 50 cases is shown in Fig. 3. This curve agrees closely with that published by Enticknap (1953). For the pulmonary arterioles the

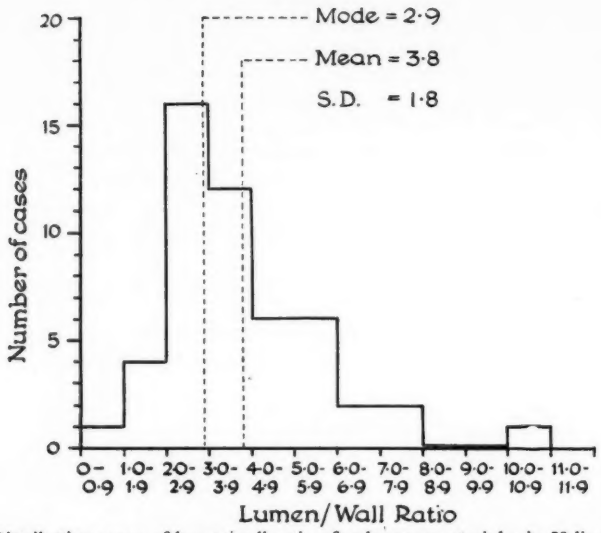


FIG. 3.—Distribution curve of lumen/wall ratio of pulmonary arterioles in 50 lingular biopsies.

normal value is about 5·5/1·0 or higher. The scatter of the curve was divided into four areas giving four arbitrary groups which are shown in Table I. Examples of pulmonary arterioles from the first and fourth groups are shown in Fig. 4 and 5.

TABLE I

	Histological Assessment	
Lumen/Wall Ratio:	10·9–8·6/1·0	1
	8·5–5·7/1·0	5
	5·6–2·9/1·0	28
	2·8–0·0/1·0	16
	Total	50

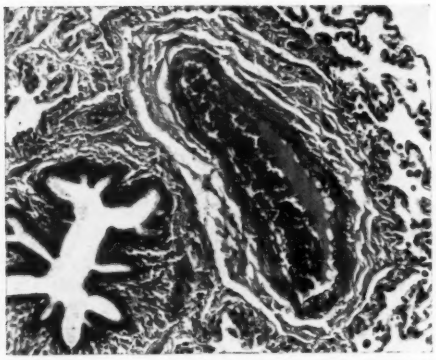


FIG. 4.—Normal pulmonary arteriole. L/W Ratio 10·3/1·0. H. and E.

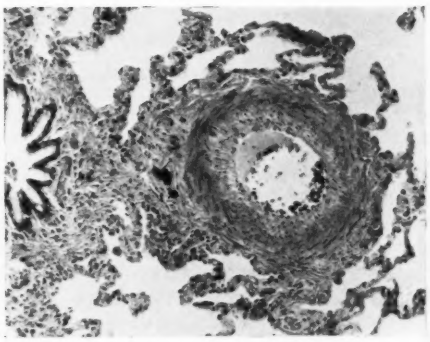


FIG. 5.—Gross arteriole damage with circular lumen and gross intimal and medial hypertrophy. L/W Ratio 2·1/1·0 H. and E.

Correlation of Groups

Each method of assessing the pulmonary arterial pressure can be compared with the three other methods. There are, therefore, six possible combinations which are indicated in Tables II, III, IV, V, VI, and VII. Since each item has been graded into four categories, it is reasonable to expect, if there is any correlation between the two items compared in each Table, that the majority of the results will lie along the diagonal extending from the bottom left corner to the top right. A scatter of one block on each side of this diagonal was allowed and the arbitrary limits have been drawn at these points.

TABLE II

Clinical Grades *v.* Pulmonary Artery Pressures

Pulmonary Artery Pressure (cms saline)	1	2	3	4	
>80	0	2	7	2	11
60–80	0	2	9	3	14
40–60	0	3	13	1	17
20–40	0	3	5	0	8
	0	10	34	6	50

Clinical Grades

TABLE III

Clinical Grades *v.* Radiological Assessment

Radiological Assessment	1	2	3	4	
Severe	0	0	8	4	12
Moderate	0	4	16	2	22
Mild	0	6	8	0	14
Nil	0	0	2	0	2
	0	10	34	6	50

Clinical Grades

TABLE IV

Clinical Grades *v.* Histological Assessment

Histological Assessment Lumen/Wall Ratio	1	2	3	4	
28·0–9/10	0	3	10	3	16
56·29/10	0	6	19	3	28
85·57/10	0	1	4	0	5
109·86/10	0	0	1	0	1
	0	10	34	6	50

Clinical Grades

TABLE V

Pulmonary Artery Pressures *v.* Radiological Assessment

Radiological Assessment	20–40	40–60	60–80	>80	
Severe	1	2	4	5	12
Moderate	1	12	7	2	22
Mild	4	3	3	4	14
Nil	2	0	0	0	2
	8	17	14	11	50

Pulmonary Artery Pressures (*cms saline*)

(1) *Clinical Gradings* (Tables II, III, and IV). These agree very closely with the radiological and histological assessment. They agree less closely with the pulmonary arterial mean pressures.

(2) *Pulmonary Arterial Mean Pressures* (Tables II, V, and VI). The gradings of this item do not agree as closely with the clinical and radiological assessments and less so with the histological assessment.

TABLE VI

PULMONARY ARTERY PRESSURES *v.* HISTOLOGICAL ASSESSMENT

Histological Assessment Lumen/Wall Ratio	20-40	40-60	60-80	> 80	
2·8-0·0/1·0	2	5	5	4	16
5·6-2·9/1·0	5	9	8	6	28
8·5-5·7/1·0	1	2	1	1	5
10·9-8·6/1·0	0	1	0	0	1
	8	17	14	11	50

Pulmonary Artery Pressures (*cms saline*)

TABLE VII

RADIOLOGICAL ASSESSMENT *v.* HISTOLOGICAL ASSESSMENT

Radiological Assessment	10·9-8·6	8·5-5·7	5·6-2·9	2·8-0·0	
Severe	0	0	6	6	12
Moderate	1	3	11	7	22
Mild	0	1	10	3	14
Nil	0	1	1	0	2
	1	5	28	16	50

Lumen/Wall Ratio
Histological Assessment

(3) *Radiological Gradings* (Tables III, V, and VII). This agrees very closely with the clinical and histological gradings but less so with the pulmonary pressure gradings, but nevertheless the correlation is present.

(4) *Histological Gradings* (Tables IV, VI, and VII). The histological assessment agrees very closely with the clinical and radiological gradings. It shows the least correlation of any of the six pairings when aligned against the pulmonary arterial pressures.

CONCLUSIONS

It appears that the criteria employed for (*a*) grading the patients clinically, (*b*) for assessing the radiological appearances with respect to pulmonary arterial pressure, and (*c*) for measuring the lumen/wall ratio of the pulmonary arterioles, correlate fairly accurately with one another.

The circumstances under which the pulmonary arterial pressure is measured at operation are somewhat artificial since the patient is under general anæsthesia, one pleural cavity is open and the patient is in lateral recumbency. It appears that the pressures thus recorded are too low, particularly in the lower grades of pulmonary hypertension in this series.

Given a recent P.A. film, we believe that an accurate statement can be made about the pathological state of the pulmonary arterial tree, the degree of disablement of the patient with mitral stenosis, and a reasonable assessment of the pulmonary arterial pressure.

REFERENCES

Baker, C., Brock, R. C., Campbell, M., and Wood, P. (1952). *Brit. med. J.*, **1**, 1043.
Enticknap, J. B. (1953). *J. clin. Path.*, **6**, 84.
Kernohan, J. W., Anderson, E. W., and Keith, N. M. (1929). *Arch. intern. Med.*, **44**, 395.
Steiner, R. E., and Goodwin, J. F. (1953). *J. Fac. Radiol.* (*Lond.*), **5**, 167.
Whitaker, W., and Lodge, R. (1953). *J. Fac. Radiol.* (*Lond.*), **5**, 182.

THE FUNCTIONAL AND CLINICAL ANATOMY OF THE MITRAL VALVE

BY

J. C. VAN DER SPUY

From the Department of Thoracic Surgery, University of Pretoria, South Africa

Received October 16, 1957

This paper is based largely on personal observations of normal and stenosed mitral valves. Some aspects that are new and some that are not in keeping with present-day concepts will be discussed.

The mitral valve is a unit that consists of a so-called fibrous "ring," of two unequal cusps, of two sets of papillary muscles, and of numerous chordæ tendineæ. When two triangular leaflets are attached at their bases to the whole circumference of a ring and their corresponding free margins are brought into apposition, then a cone is formed. The mitral valve consisting, as it does, of two cusps, each somewhat triangular and each attached at its base to the mitral ring, is, therefore, when the cusp margins are in contact, cone-shaped. The significance of and the necessity for an "elongated" mitral "cone" was appreciated by William Harvey in 1628.

In a cone-shaped valve, marginal contact alone would not give the same firm and complete valve closure as would total obliteration of the lumen of the cone when there is complete contact between the inner surfaces of the cusps. To obtain such surface contact a force is required to act on the cone from below. This force is the intraventricular systolic pressure. The mitral valve is a flat cone. Had it been a circular cone, then considerable excursion of the cusps, with more wear and tear, and an unduly high subvalvular pressure, and therefore a high systemic pressure, would have been required to close the lumen of the valve-cone during systole.

The antero-medial cusp is a hinged extension into the cavity of the left ventricle of the postero-lateral aortic root. The hinge is the corresponding antero-medial half of the mitral "ring" and is formed by the common fibrous origins of the postero-lateral half of the aortic root, of the antero-medial cusp, and the major part of two aortic cusps. As the base of this mitral cusp is attached to the origin from the aortic root of two adjacent aortic cusps, the antero-medial half of the mitral "ring" is bi-concave (Fig. 1). Had the antero-medial half of the mitral "ring" been semi-circular or semi-ovoid, then the entire base of the antero-medial cusp could not have hinged on the entire postero-lateral half of the root of the aorta.

The postero-lateral half of the mitral "ring" is formed by the common fibrous origins of the postero-lateral cusp and of the corresponding part of the left atrium and of the base of the left ventricle (Fig. 2). (The anterior half of the left atrium has a fleshy origin from the upper surface of the base of the antero-medial cusp close to the mitral "ring.") As the base of the left ventricle is concave, the base of the postero-lateral cusp is convex; thus the shape of the posterior half of the mitral "ring" is semi-ovoid. Had the mitral "ring" occupied the whole of the base of the left ventricle, then its posterior half would have been semi-circular.

The two papillary muscle groups arise from the wall of the ventricle opposite, but distal to, the commissural margins of the cusps. They are therefore known as the antero-lateral and the postero-medial groups. Whereas their bases are attached to the ventricle at about the junction of the upper and middle thirds, their apices project into the upper third of the ventricular cavity and come to lie somewhat close to the commissural margins of the cusps.

The chordæ tendineæ fan out from the apical zones of one group of papillary muscles to be attached to the margins and under surfaces of the ipso-lateral halves of the cusps. By approximating the apical and commissural zones of the cusps they convert the ring-and-cusp unit into a cone-shaped valve. The more cranial members pass somewhat more steeply towards the upper commissural margins and under surfaces, whereas the more caudally placed chordæ tendineæ pass more horizontally towards the apical zones of the cusps. The more centrally placed chordæ tendineæ of the antero-medial cusp appear somewhat thicker and stronger (Sokoloff *et al.*, 1950) and are attached to the cusp at right angles to the margins of the mitral cone (Fig. 3). During diastole the hinged antero-medial cusp swings downwards and forwards into the path of the left ventricular outflow. Tension exerted on these strong chordæ tendineæ by the papillary muscles during early systole draws the antero-medial cusp towards the postero-lateral one and so prevents its displacement towards the aortic root by the high ejection force of left ventricular systole. Subsequent tension on these chordæ tendineæ will exert a flattening force on the mitral cone.

FIG. 1.—The bi-concave base of the antero-medial cusp is attached to the bi-convex postero-lateral half of the root of the aorta.

The nature of the distribution of the attachments of the chordæ tendineæ to the ventricular surface of the cusps plays a most important role in the mechanism of mitral valve closure. These chordæ tendineæ of the antero-medial cusp are attached only to the peripheral zone of the cusp (Fig. 4). The basal somewhat trigonal portion of the antero-medial cusp is therefore much thinner than the peripheral portion and its excursion towards the atrium during systole is not directly restricted by the chordæ tendineæ. This mobile "trigone" can therefore billow towards the cavity of the left atrium during systole (Fig. 5). The chordæ tendineæ of the postero-lateral cusp, however, are inserted into its entire ventricular surface, excluding the basal zone (Fig. 6). The base of the cusp, therefore, being more mobile than the rest of the cusp, bulges forwards during systole and causes flattening of the valve by reducing the postero-anterior diameter of the base of the cone, thus reducing the degree of cusp excursion required to cause total obliteration of the lumen of the valve cone. As the base of the postero-lateral cusp is attached to a segment of the base of the left ventricle via the mitral "ring," this basal portion of the cusp remains concave during systole.

The antero-medial cusp is much longer than the postero-lateral one (Fig. 7). The mitral cone, therefore, has an oblique base, i.e. the mitral "ring" is set obliquely. Had the cusps been of equal length, then complete flattening of the base of the cone would have been necessary for total cusp surface contact, i.e. total valve closure, to have taken place. Instead the antero-medial cusp is long and its thin mobile "trigone" lies opposite the concave base of the postero-lateral cusp. In systole, therefore, the former billows upwards and backwards to fit snugly into the concavity of the latter, resulting in complete valve cone closure (Fig. 5).

As the postero-lateral root of the aorta, from which the antero-medial cusp is suspended, is convex posteriorly, the mitral "ring," as seen from above, is somewhat kidney-shaped (Fig. 8). In the neutral position the body of the antero-medial cusp, therefore, has a natural tendency to bulge towards the concavity of the postero-lateral cusp. As the antero-medial cusp is suspended from the aortic root it can readily swing backwards and forwards in systole and diastole, and as the mobile "trigone" lies opposite the posterior half of the mitral "ring," the mouth of the cone at this level is an oval opening in diastole and a crescentic slit in systole (Fig. 5).

The base of the left ventricle accommodates the circular (as seen from above) root of the aorta and, lying postero-lateral to it, the kidney-shaped mitral "ring" (Fig. 9). During systole the base

FIG. 2.—The postero-lateral half of the mitral "ring" gives attachment to the corresponding portions of the base of the left ventricle and of the left atrium and to the postero-lateral cusp.

FIG. 3.—The chordæ tendineæ fan out from the apical regions of the papillary muscles to be attached to the margins and ventricular surfaces of the ipso-lateral halves of both cusps. The central group of chordæ tendineæ of the antero-medial cusp are thick and strong and are attached to the cusp at right angles to its commissural margin.

FIG. 4

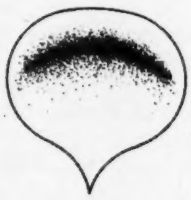


FIG. 5

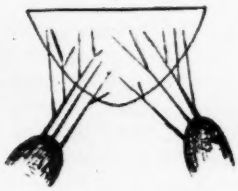


FIG. 6

FIG. 4.—The surface chordæ tendineæ of the antero-medial cusp are attached to the peripheral zone of the cusp only.

FIG. 5.—During systole the mobile "trigone" of the antero-medial cusp fits snugly into the concavity of the mobile base of the postero-lateral cusp. The mouth of the cone is a crescentic slit in systole.

FIG. 6.—The surface chordæ tendineæ of the postero-lateral cusp are attached to its entire ventricular surface.

of the left ventricle is reduced in circumference (Brock, 1952). Simultaneously the elastic aorta, subjected to the full force of the blood ejected by the left ventricle, expands. As the antero-medial cusp is attached to the postero-lateral root of the aorta, and as the postero-lateral cusp is attached to the base of the left ventricle, ventricular systole produces flattening of the mitral "ring" with consequent approximation of the cusps.

FIG. 7

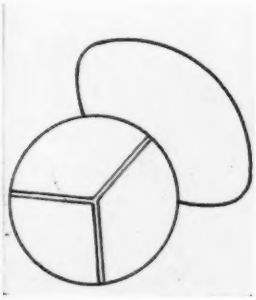


FIG. 8

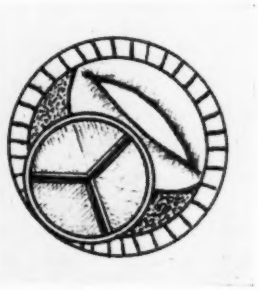


FIG. 9

FIG. 7.—The antero-medial cusp is much longer than the postero-lateral one. As the apical zones of the cusps correspond, the cone has an oblique base.

FIG. 8.—As the postero-lateral root of the aorta, from which the antero-medial cusp is suspended, is convex posteriorly, the mitral "ring," as seen from above, is somewhat kidney-shaped.

FIG. 9.—The base of the left ventricle accommodates the circular (as seen from above) root of the aorta and the kidney-shaped mitral "ring."

The Normal Mechanism of Mitral Valve Closure

When, at the onset of systole, the pressure in the left ventricle exceeds that in the left atrium, mitral valve closure is brought about by a series of mechanisms which act either simultaneously or in very rapid succession.

As a result of the rising subvalvular tension, and as a result of the pull by the papillary muscles on the chordæ tendineæ, the antero-medial cusp, hinged at the aortic root, rotates backwards and the postero-lateral cusp, hinged at the posterior half of the mitral "ring," rotates forwards. This cusp rotation is brought to a halt after a very brief moment when the apical and commissural margins of the cusps meet. From this moment onwards the mitral valve is closed, although not firmly so. As there is a progressive rise in the left ventricular pressure, so there is a progressive increase in the extent of cusp surface contact (Fig. 10); and as the thin and mobile "trigone" of the antero-medial cusp balloons upwards and backwards towards the concave base of the postero-lateral cusp, so the mobile base of the postero-lateral cusp is forced against the ballooning antero-medial cusp, resulting in complete valve closure. Fig. 11 indicates how flattening of the mitral

FIG. 10.—Rise in the left ventricular pressure causes progressive increase in the extent of cusp surface contact.

FIG. 11.—Flattening of the mitral "ring" between the root of the aorta and the base of the left ventricle.

"ring" between the root of the aorta and the base of the left ventricle causes an increase in the extent of cusp surface contact.

From the above description it will be seen that the construction of the mitral valve is such that it closes by means of progressive cusp surface contact in a direction from the apex towards the base of the valve, i.e. the antero-medial cusp rolls on the postero-lateral cusp from the latter's apex towards and as far as the latter's base. The principle involved is the same as is employed by, e.g. wrestlers when adopting a rolling motion to break the force of a fall when striking the mat. Had the cusps been vertical leaflets, meeting head on in systole, then the contact force would have been twice that of left ventricular pressure. The rolling mechanism of mitral valve closure is therefore of the greatest importance in protecting the cusps against injury by the high left ventricular pressure. As the antero-medial cusp is for practical purposes a direct continuation of the corresponding portion of the aorta into the cavity of the left ventricle, it can be readily appreciated how the systolic force which causes rolling mitral valve closure "rolls" off the under surface of the antero-medial cusp into the lumen of the aorta.

The Mechanism whereby Stenosis of the Mitral Valve is Produced

During diastole the commissural margins of the cusps form the sides of a triangular opening, the apex of which is close to the mitral "ring." During systole the commissural margins of the cusps are in apposition and this triangular space is obliterated. Although there are very brisk and forceful backward and forward movements of these commissural margins during systole and diastole, the very apex of the triangular space remains relatively immobile. Material deposited in the acute angle of this immobile apex will cause fusion between the adjacent commissural margins in rheumatic heart disease. With progressive silting up (Tweedy, 1956) of the apex of this triangular diastolic opening, a stage is reached when the further deposition of material in the apex results in its replacement by a concave margin. It would, therefore, appear that the somewhat constant size of 1 by $\frac{1}{2}$ cm. and the oval shape of the opening of a fully stenosed mitral valve (Brock, 1952) are determined by the gradual replacement of the acute commissural angle on either side of the stenosing opening by a concave margin which brings the silting up process to an end. The size of the opening does not appear to depend on fusion between the commissural margins secondary to fusion at centrally-situated critical areas of tendon insertion as postulated by Brock (1952).

Closing Mechanism of a Stenosed Valve

Examination of an autopsy specimen of a fully stenosed mitral valve will show such a valve to be, anatomically, incompetent also. But it is well known that a tightly stenosed valve is only rarely associated with significant incompetence. What then is the mechanism preventing functional incompetence in an anatomically incompetent valve? As explained above, mitral valve closure is normally brought about in the first instance by apical and commissural zone contact followed by cusp surface contact in a direction from the apex of the cone towards, and as far as, the base of the postero-lateral cusp. Because of the presence of the firm oval opening at the apex of the closing mitral valve, marginal contact cannot take place in this region. Nor can surface contact close the lumen of the apical zone. As the left ventricular pressure rises, so the cusps are forced closer and closer together, causing a progressive reduction in the antero-posterior diameter of the supra-stenotic valve lumen, until finally the cusps meet above the opening to obliterate the lumen of the basal part of the cone, thus preventing prolonged regurgitation through the rigid and anatomically incompetent apex of the valve.

Supra-stenotic valve closure appears to be wholly responsible for the production of the "presystolic" murmur, whereas supra-stenotic cusp surface contact seems to be partly responsible for the characteristic delayed (Cossio and Berconsky, 1943) and accentuated (Dock, 1933) first heart sound. It is believed that the presystolic murmur results from an increased blood flow through the narrowed mitral orifice towards the end of diastole (Wood, 1956). Whereas valve closure normally starts at the margins of the cusps at the onset of systole, in mitral stenosis these margins

are fused except at the apex, where a firm oval opening is interposed, and valve closure only takes place during early systole by means of supra-stenotic cusp surface contact. This means that in mitral stenosis the valve apex is still open at a time when normally it is closed and that regurgitation takes place during early systole through a progressively decreasing supra-stenotic valve lumen. As there is a progressive decrease in the antero-posterior diameter of the lumen, so there is a progressive rise in the left ventricular pressure and, therefore, in the force and rate of flow of the systolic regurgitation until supra-stenotic valve closure finally takes place (Fig. 12). The characteristic "presystolic" crescendo murmur so produced, therefore, appears to be caused by regurgitation during early ventricular systole. As the murmur precedes the first heart sound, produced by delayed supra-stenotic valve closure, it appears to occur prior to ventricular systole.

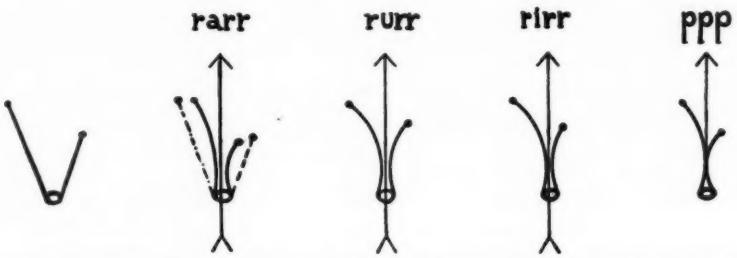


FIG. 12.—In mitral stenosis regurgitation takes place during early systole through a progressively decreasing supra-stenotic valve lumen. As there is a progressive decrease in the antero-posterior diameter of this lumen, so there is a progressive rise in the left ventricular pressure and, therefore, in the force and rate of flow of the systolic regurgitation, until supra-stenotic valve closure takes place, producing the characteristic "presystolic" crescendo murmur.

If the mechanism of supra-stenotic valve closure is accepted, then it becomes obvious that the direction of the blood flow during early systole through the closing valve is from the left ventricle into the left atrium. Then the "presystolic" murmur cannot be produced by atrial systole in late diastole. The "presystolic" murmur, therefore, appears to be a pre-delayed-first-sound ventricular systolic murmur. Had the direction of flow of the blood which causes the "presystolic" murmur been from the left atrium towards the left ventricle, then there would have been a short break between the end of the murmur and the first sound, representing the time required for valve excursion from the diastolic to the systolic position. Then the "presystolic" murmur would not have ended with an accentuated first sound (Wood, 1956). The length of the "presystolic" murmur seems to depend on the rate of excursion and mobility of the cusps, on the length of the antero-posterior diameter of the stenosed opening and on the presystolic position of the cusps.

During diastole the outflow from the left atrium is partially obstructed and the cusps, fused at their margins, are forced downwards into the cavity of the ventricle. The presystolic position of the cusps is determined by the length of diastole. When the ventricular filling time is short, the cusps are still maximally displaced towards the ventricle, and ventricular systole causes maximal and rapid cusp excursion towards the atrium with the production of a loud first sound. When diastole is long, blood filling the ventricular cavity slowly approximates the cusps, and when ventricular systole occurs, minimal cusp excursion causes valve closure with the production of a soft sound (Dock, 1933). It would seem, however, that this wide range of cusp excursion is not the only reason why the first sound is accentuated in mitral stenosis. As supra-stenotic valve closure implies late cusp surface contact, the valve is closed by a left ventricular pressure that is higher than the pressure that normally causes valve closure. Also, as the rolling mechanism which breaks the force of cusp contact is upset, owing to the interposition of the stenosed opening at the apex of the valve, the cusp closing force is distributed over a smaller cusp contact area, and the cusps meet more or less head on. As, therefore, the cusp-closing force is high, the contact surface reduced, and the direction of contact head on, the first sound in mitral stenosis is characteristically loud, abrupt, and high-pitched.

Mitral valve closure in mitral stenosis is delayed because early ventricular systole does not cause cusp excursion towards the closed position, but, as the left atrial pressure in such cases is elevated, it merely overcomes the pressure gradient across the mitral valve (Cossio and Berosky, 1943). Only after the pres-

sures on either side of the valve have become equal will further ventricular systole result in valve closure. This delay is indicated by an increase in the time interval between the onset of the QRS complex of the electrocardiogram and the first heart sound of the phonocardiogram (Wells, 1954). Kelly (1955) examined this Q–1 interval in 100 patients with cardiac lesions of all types, except those involving the mitral valve, and in 75 patients with mitral stenosis as the only lesion. He concluded that with a Q–1 interval of longer than 0·07 second a mitral stenosis of significant degree could be taken for granted. It is suggested, however, that the mechanism of valve closure in mitral stenosis, namely supra-stenotic cusp surface contact in early systole, is a contributory cause of the increased Q–1 interval.

In atrial fibrillation the presence or absence of the murmur depends on the length of diastole (Messer *et al.*, 1951). When diastole is long the mid-diastolic murmur begins with the opening snap and fades out completely before the first heart sound. If diastole is short, the murmur, beginning in the same way, lasts throughout diastole to the very beginning of the first heart sound; and "since the first sound is delayed, the murmur is not only presystolic, but actually extends for a short interval after the beginning of electrical systole." When diastole is short the cusps are still maximally displaced towards the left ventricle when systole takes place (Dock, 1933). Then there will be maximal systolic regurgitation through the apex of the mitral cone until supra-stenotic valve closure takes place. When diastole is long there is a greater filling of the left ventricle and the cusps will float towards the closed position and, when systole occurs, only slight excursion of the cusps is required to produce supra-stenotic valve closure with the production of a soft first heart sound (Dock, 1933) and an absent pre-delayed-sound murmur.

In cusps of normal length, supra-stenotic cusp surface contact is limited by two important factors, namely by thickening of the cusps and by shortening of the chordæ tendineæ. It is obvious that thickening of the cusps, through fibrosis or calcification, will reduce the systolic excursions of the mobile "trigone" of the antero-medial cusp and of the mobile base of the postero-lateral cusp and so interfere with normal valve function. Shortening of the chordæ tendineæ, too, is a most important cause of regurgitation, whether the valve be stenosed or not. During mitral valve closure the apex of the cone is necessarily displaced upwards towards the atrium, but this cannot take place because of shortening of the chordæ tendineæ which results in the cusp remaining more or less straight during systole, i.e. valve closure cannot take place.

As supra-stenotic valve closure fails, so various degrees of regurgitation will occur. The degree of regurgitation and the extent of cusp surface contact are inversely proportional. Therefore, provided the thickness and the mobility of the cusps remain constant, there is an inverse proportion between the loudness of the first sound and the extent of the leak. Thus when the mitral sound is loud and snapping there will be no, or only minimal, mitral regurgitation and the sound heard on auscultation will be *rrruppp*. Similarly the murmur of combined mitral stenosis and regurgitation may be *rrrupps*, *rrupthth* or *rrushshsh*. As the "*p*" representing cusp surface contact decreases, so the systolic murmur increases. The character of the first heart sound in mitral stenosis depends largely on the heart rate (Wynn, 1953). When there is rapid cusp excursion from the fully open to the closed position of the valve, supra-stenotic cusp surface contact improves. Thus after even slight exertion the murmur *rrupthth* of combined stenosis and regurgitation may, for example, change to the murmur *rrruppp* of pure stenosis. It therefore seems that auscultation to determine the presence of mitral regurgitation in association with stenosis will be reliable only when done under basal conditions. In this respect it is of interest to note that although a stenosed valve may be incompetent when the subject is at rest, the incompetence may disappear completely when he is active.

Summary and Conclusions

The posterior half of the mitral "ring" is semi-ovoid; its anterior half is bi-concave. The papillary muscles and chordæ tendineæ prevent prolapse of both cusps into the cavity of the left atrium and of the antero-medial cusp towards the root of the aorta; they convert the cusp-and-"ring" unit into a cone, which they help to flatten during systole.

The surface chordæ tendineæ of the antero-medial cusp are attached only to the marginal zone of its ventricular surface. Those of the postero-lateral cusp are attached to the entire ventricular surface of the cusp excepting the basal zone.

The billowing "trigone" of the long antero-medial cusp fits snugly into the bulging concave base of the shorter postero-lateral cusp. During systole the mitral "ring" becomes flattened between the postero-lateral root of the aorta and the base of the left ventricle. During mitral valve closure the antero-medial cusp rolls on the postero-lateral cusp in a direction from its apex towards, and as far as, its base, thereby reducing the cusp contact force.

The mechanism whereby mitral valve stenosis is produced is discussed. Anatomically the stenosed mitral valve is also incompetent. Functional incompetence, however, is prevented by means of supra-stenotic cusp surface contact.

The "presystolic" murmur appears to be an early systolic murmur occurring prior to a delayed first sound. The length of the "presystolic" murmur seems to depend on the rate of excursion and mobility of the cusps, on the length of the antero-posterior diameter of the stenosed opening, and on the presystolic position of the cusps.

The accentuated first sound is caused not only by the increased span of cusp excursion in systole, but also by delayed (i.e. supra-stenotic) cusp surface contact and by a disturbance of the rolling mechanism of valve closure. The result is that the cusps are closed by a higher systolic force distributed over a smaller contact area of cusps now meeting more or less head on. The first sound delay is caused not only by the pressure gradient across the mitral valve but also by the delayed (i.e. supra-stenotic) cusp surface contact.

In atrial fibrillation the presence of the pre-delayed-sound murmur depends on the presystolic position of the cusps.

In cusps of normal length supra-stenotic cusp surface contact is reduced by thickening of the cusps and by shortening of the chordæ tendineæ. As supra-stenotic cusp surface contact decreases, so mitral incompetence increases.

I wish to express my thanks to Mr. Theo Marais for the photographs and to Miss S. Kloppers for the drawings.

References

Brock, R. C. (1952). *Brit. Heart J.*, **14**, 489.
Cossio, P., and Berconsky, I. (1943). *Rev. Argent. Cardiol.*, **10**, 162.
Dock, W. (1933). *Arch. intern. Med.*, **51**, 737.
Harvey, W. (1628). *The Works of William Harvey*. Sydenham Society, London, 1847, p. 80.
Kelly, J. J., Jr. (1955). *Amer. Heart J.*, **19**, 862.
Messer, A. L., Counihan, T. B., Rappaport, M. B., and Sprague, H. B. (1951). *Circulation*, **4**, 576.
Sokoloff, L., Elster, S. K., and Righthand, N. (1950). *Circulation*, **1**, 782.
Tweedy, P. S. (1956). *Brit. Heart J.*, **18**, 173.
Wells, B. (1954). *Brit. Heart J.*, **16**, 261.
Wood, P. (1956). *Diseases of the Heart and Circulation*. Eyre and Spottiswoode, London.
Wynn, A. (1953). *Brit. Heart J.*, 15, 214.

RESIDUAL LUNG VOLUME IN MITRAL DISEASE

BY

R. GARBAGNI, P. F. ANGELINO, A. BRUSCA, AND E. MINETTO

From Instituto di Patologia Speciale Medica e Metodologia Clinica dell'Università di Torino. Direttore: Prof. G. C. Dogliotti

Received January 6, 1958

The degree of lung distension during quiet respiration, the so-called respiratory position or resting expiratory level, is essentially determined by a balance between the passive forces produced by the thoracic wall and the active forces due to the elastic properties of the lung. Therefore the interplay of these forces has a direct role in determining the extent of the functional residual capacity and, consequently, of the residual lung volume.

Previous work (Heyer *et al.*, 1948; and Mack *et al.*, 1947) has demonstrated that pulmonary vascular congestion does induce a certain degree of lung stiffness, and in addition pulmonary congestion is a constant finding in mitral valve disease. In view of the relationships between functional residual capacity on the one hand, and lung stiffness and pulmonary congestion on the other, this investigation was carried out with the purpose of studying the functional residual capacity in a large series of patients with pulmonary engorgement due to mitral disease.

Material and Methods

This study was carried out in 60 patients, classified as follows. Group 1 consisted of 32 patients with tight pure mitral stenosis and usually severe dyspnœa on effort, but without any evidence of congestive heart failure at rest; 17 of these patients were women and 15 men. Their ages ranged from 21 to 49 years (mean age=35·5 years).

Group 2 consisted of 18 subjects with pure tight mitral stenosis and signs of congestive heart failure at rest; in this group there were 12 women and 6 men. The age of these patients varied between 22 and 49 years, with a mean age of 35·3 years.

Group 3 consisted of 10 patients with predominant mitral regurgitation. Functional capacity was good in two, while in the remaining eight severe dyspnœa was present at rest and/or on mild effort. Seven patients of this group were women and three were men; their age varied between 16 and 47 years (mean age=32 years).

The clinical diagnosis was confirmed by digital exploration of the mitral valve during valvotomy or surgical repair of valvular insufficiency.

Functional residual capacity (F.R.C.) was determined with the closed circuit method according to van Veen *et al.* (1952): helium was used, as proposed by Briscoe (1952), Pillot (1955) and others. By this technique it is possible to measure the intrapulmonary time of mixing, an index of the uniformity and efficiency of the intrapulmonary ventilation.

The expiratory reserve volume determined at the end of the test was subtracted from the observed F.R.C.; the difference between the two represented the residual volume (R.V.).

The lung volumes were corrected to body temperature, ambient pressure, and saturation (B.T.P.S.).

In normal subjects, both men and women, residual volume, as a percentage of total lung capacity (T.L.C.), varies according to the age of the subject as follows (Baldwin *et al.*, 1948):

R.V./T.L.C.=20% between the age of 16 and 34 years.
R.V./T.L.C.=23·4% between the age of 35 and 49 years.
R.V./T.L.C.=30·8% between the age of 50 and 69 years.

As an index of residual volume we used this ratio between residual volume (R.V.) and the observed total lung capacity (T.L.C.). Values of this ratio higher than 30 per cent are considered to be abnormal (Gordon, 1957).

If the theoretical value of vital capacity is known for a given patient, the theoretical absolute values of R.V. and T.L.C. can be calculated from the ratio R.V./T.L.C. However, because of the great approximation ($\pm 20\%$) of the theoretical values of V.C., it is evident that calculation of absolute theoretical values for R.V. and T.L.C. is practically meaningless. It is for this reason that the ratio R.V./T.L.C. should be used as the only reliable index of the R.V. in a given patient.

Results

In patients with tight mitral stenosis, without clinical evidence of combined heart failure, mean values were as follows:

Total lung capacity	=ml. 5,350±1,140
Functional residual capacity	=ml. 3,290±1,900
Expiratory reserve volume	=ml. 1,190±450
Residual volume	=ml. 2,090±700
R.V./T.L.C. × 100	=38±7

When the ratio R.V./T.L.C. × 100 was studied according to the age of the patients, the following mean values were calculated:

age <30 years R.V./T.L.C. × 100=36±6
age 30–39 years R.V./T.L.C. × 100=39±8
age >40 years R.V./T.L.C. × 100=41±7

The "mixing time" was in each instance equal to, or less than three minutes. This value, with our technique, is well within normal limits.

In patients of group II, in whom tight mitral stenosis and combined heart failure were present, we observed the following mean values:

Total lung capacity	=ml. 4,460±1,280
Functional residual capacity	=ml. 2,900±720
Expiratory reserve volume	=ml. 1,010±280
Residual volume	=ml. 1,890±570
R.V./T.L.C. × 100	=42±8

The ratio R.V./T.L.C. varied, according to the age, as follows:

age <30 years R.V./T.L.C. × 100=39±6
age 30–39 years R.V./T.L.C. × 100=41±8
age >40 years R.V./T.L.C. × 100=44±11

The "mixing time" was normal.

The values observed in the two patients with predominant mitral regurgitation and no evidence of heart failure were as follows:

Total lung capacity	=ml. 4,940 and c.c. 5,440
Functional residual capacity	=ml. 3,140 and c.c. 3,570
Expiratory reserve volume	=ml. 1,080 and c.c. 980
Residual volume	=ml. 2,060 and c.c. 2,600
R.V./T.L.C.	=41 and 47

In the other 8 subjects with mitral regurgitation and clinical evidence of heart failure we found the following values:

Total lung capacity	=ml. 4,110±700
Functional residual capacity	=ml. 2,580±800
Expiratory reserve volume	=ml. 890±280
Residual volume	=ml. 1,700±500
R.V./T.L.C. × 100	=41±9

A normal "mixing time" was again found.

It is evident from our results that residual lung volume as measured by the ratio R.V./T.L.C. is constantly increased in mitral valvular disease. These changes seemed to be greater in the patients of the older age groups.

A slightly different behaviour was observed between the patients with tight mitral stenosis without right heart failure and those with the same valvular lesion and evidence of right and left heart failure.

In both groups R.V. was increased approximately to the same extent; but T.L.C. in the decompensated group was decreased due to a diminution of the expiratory reserve volume. Therefore the ratio R.V./T.L.C. was slightly higher; this difference, however, was not statistically significant, nor was the difference between mean values of R.V. in these two groups of patients.

In patients with predominant mitral regurgitation, R.V., T.L.C., and the ratio between the two parameters showed changes similar to those observed in the previous groups.

Discussion

Our observations confirm previous reports on the expansion of the residual lung volume in mitral disease (Mathieu *et al.*, 1953; Castaing *et al.*, 1952; van Bogaert *et al.*, 1955; and Englert *et al.*, 1956).

Several explanations have been put forward to explain the changes observed. According to Mathieu (1953), the increased residual volume must be considered as a consequence of the pulmonary congestion with the superimposed broncho-pulmonary reactive fibrosis, lung hæmosiderosis, bronchial inflammation, and upper respiratory infections. All these factors would eventually lead to a loss of elasticity of the lung, and to an anatomical and functional situation comparable to early pulmonary emphysema.

Each one of the factors that we have listed above certainly contributes in some way to the pathogenesis of the increased residual volume in mitral valvular disease. However, in these conditions it never reaches the extent usually observed in pulmonary emphysema. Furthermore the normal mixing time in mitral patients indicates that in these subjects the ventilatory situation must be different from the one present in pulmonary emphysema, in which the distribution of inspired air is severely impaired and the mixing time is greatly prolonged.

Castaing *et al.* (1952) maintain that the increased R.V. results from a ventilatory hyperactivity, as a compensatory mechanism for the impaired hæmatosis. The functional situation of the lung in mitral patients would then be comparable to the compensatory hyperactivity of the spared lung after pneumonectomy. The pulmonary distension of the mitral lung, contrary to what is observed in emphysema, should then be considered as a favourable mechanism by which the respiratory performance is improved and only its prolonged duration could eventually lead to a permanent stiffness of the pulmonary parenchyma.

However, Marshall *et al.* (1954) and Christie (1953) have demonstrated that ventilatory work in patients with mitral stenosis at rest is much increased, due to the loss of the elastic properties of the lungs.

Two mechanisms may be responsible for the rigidity of the lung. The hypertensive pulmonary arterial tree can, by itself, be considered a more rigid framework for the lung (Mack, 1947). Interstitial œdema and, subsequently, the fibrotic interstitial proliferation are the obvious organic causes of lung stiffness.

Due to the loss of its elastic properties, the lung cannot return to a normal resting expiratory level; the tidal volume encroaches on the inspiratory reserve volume. It follows that the resultant rapid shallow breathing with increased residual lung volume represents an adaptation to the increased stiffness of the lung.

Summary

The residual lung volume was found to be constantly increased in 60 patients with mitral valvular disease. These changes have been attributed to a loss of the elastic properties of the lung.

In this respect the increased residual volume may represent an important link in the pathogenesis of cardiac dyspnœa.

References

Baldwin, E. de F., Cournand, A., and Richards, D. W., Jr. (1948). *Medicine*, Baltimore, **27**, 243.
Briscoe, W. A. (1952). *Clin. Sci.*, **11**, 45.
Castaing, R., Bricaud, H., Broustet, P., and Marty, J. (1952). *Arch. Mal. Cœur*, **45**, 724.
Christie, R. V. (1953). *Proc. Roy Soc. Med.*, **46**, 381.
Englert, M., and Denolin, P. (1956). *Acta cardiol.* (*Brux.*), **11**, 365.
Gordon, B. L. (1957). *Clinical Cardiopulmonary Physiology*. Grune and Stratton, New York, London.
Heyer, H. E., Holman, J., and Shires, G. T. (1948). *Amer. Heart. J.*, **35**, 463.
Mack, J., Grossman, M., and Katz, L. M. (1947). *Amer. J. Physiol.*, **150**, 654.
Marshall, R., McIlroy, M. B., and Christie, R. V. (1954). *Clin. Sci.*, **13**, 137.
Mathieu, L., Grilliat, J. P., and Pillot, P. (1953). *Arch. Mal. Cœur*, **46**, 341.
Pillot, P. (1954). *Les Variations du Volume Pulmonaire Résiduel*. Thèse de Nancy, n. 30.
Van Bogaert, A., Vandael, J., van Genabeek, A., and van der Henst, H. (1955). *Arch. Mal. Cœur*, **48**, 225.
Van Veen, G., Orie, N. G. M., and Hirdes, J. J. (1952). *Acta tuberc. scand.*, **26**, 251.

THE ELECTROCARDIOGRAM IN SYPHILITIC HEART DISEASE

BY

GEOFFREY STOREY

From the Cardiac Department of the London Hospital

Received October 31, 1957

The greater incidence of syphilitic heart disease is in late acquired syphilis and there is no evidence that the heart is involved during the early stage of the infection, though this is less certain in congenital syphilis. The aortitis of late acquired syphilis usually starts above the aortic valve and may spread upwards, producing weakness of the wall of the aorta and resulting in aneurysm formation; aortic incompetence may then result from stretching of the aortic ring. The syphilitic process, however, more commonly spreads down to involve the aortic cusps, producing aortic incompetence from valvitis. In either case the orifices of the coronary vessels may be narrowed (although this does not often occur in the presence of aneurysm alone).

Abnormalities of the electrocardiogram result from left ventricular hypertrophy following aortic incompetence or as a result of cardiac ischæmia from stenosis of the coronary orifices. Whether the heart itself is commonly involved by an inflammatory lesion has been much discussed; certainly gummata of the heart occur, either as a single gumma or as a diffuse infiltration, but are rare. Opinion still varies as to whether the patchy fibrosis found in the myocardium is caused by stenosis of the coronary orifices or by syphilitic myocarditis, but the former explanation is now the most favoured.

There is no agreement on the importance of the electrocardiogram in the diagnosis of stenosis of the coronary orifices and this work was undertaken to investigate this problem.

In congenital syphilis it is clear from the reports of various authors that although the *Treponema pallida* is found in the heart there is no reaction to it by the tissue. Similarly several reports are available on the findings in early adult syphilis and most authors (Turner and White, 1927; Ingraham and Maynard, 1930; Chamberlain and Follows, 1933; Annett, 1928) agree that there are no certain electrocardiographic abnormalities. More recently Klotz and Crede (1945) found only four cases among 100 cases of early syphilis with some abnormality of the T waves.

In late syphilis, abnormalities of the cardiogram have been frequently described, but the criteria of such abnormalities are not now acceptable. Thus, the differentiation of ischæmic changes from left ventricular preponderance was not then made, while left ventricular preponderance was often inferred from left axis deviation only. Other abnormalities that have been described are auriculo-ventricular dissociation, bundle-branch block, and slurring of the QRS.

Heimann (1927) described notching of the R wave in limb leads which he believed was specific of syphilitic heart disease. The specificity of the notch has not been confirmed by later writers although slurring and notching of the QRS is often described, and Evans and McRae (1952) believe that notching of the QRS in CR7, even in the presence of left ventricular preponderance, signifies ischæmia.

Juster and Pardee (1929) were the first to relate cardiographic abnormalities to ostial stenosis, and reported T wave changes that they attributed to this in 18 per cent of their cases; they correlated these with post-mortem findings. Coombs (1932), reviewing the subject, collected the findings in 276 cases, and noted the divergent opinions expressed by the various authors and concluded that the cardiogram was of little value in the diagnosis of coronary orifice occlusion. Several authors have agreed with this. Bruenn (1934) reported no difference between the cardiogram in cases with much stenosis of the coronary orifices and those with little or no stenosis. Smith and Blackford (1938) found little difference between the cardiogram in cases with and those without pain in the chest, while Burch and Winsor (1942) agreed with this.

It should be appreciated, however, that chest lead electrocardiography was only in its infancy then. Sprague (1942), describing 22 cases of syphilitic heart disease examined at necropsy, found narrowing of the ostia in three out of four cases of bundle-branch block. He also drew attention to the fact that atheroma of the coronary arteries might be co-existent with syphilitic heart disease, as already noted by Gallavardin (1932), and might be responsible for abnormalities in the cardiogram.

Most authors agree that stenosis of the coronary orifices rarely causes a large area of cardiac infarction. Parsonnet and Bernstein (1943) and Jones and Bedford (1943) comment on the rarity of the finding of Q waves in syphilitic heart disease.

The introduction of the exercise test is a further aid in the recognition of coronary ostial stenosis, and Berk (1941) found it valuable, particularly in syphilitic patients under 45 years of age, where coronary atheroma was less likely to be a complicating factor.

Apart from the effects of cardiac ischæmia and hypertrophy of the left ventricle, cardiographic abnormalities may occur rarely from the presence of gummata in the myocardium; these may take the form of a single gumma or a diffuse gummatous infiltration. The cardiographic abnormalities take the form of a conduction defect with alteration in rhythm.

In recent years much attention has been paid to the various types of cardiographic patterns produced by interference with the blood supply to the myocardium. Master *et al.* (1944) have differentiated a syndrome of coronary insufficiency from that of cardiac infarction. This is characterized by S–T depression or T wave inversion without Q waves or S–T elevation. They mention stenosis of the coronary orifices from syphilis as a cause of this syndrome. The electrocardiographic changes may be transient, and they attribute the S–T depression to the subendocardial localization of the lesion. Yu and Stewart (1950) have supported this view. Levine and Ford (1950) believe that the subendocardial region is the most likely to suffer in any condition that causes depression of the total coronary flow, and Evans and McRae (1952) have described various lesser changes in the S–T and T wave that indicate such coronary arterial interruption.

Material and Method

Seventy-two patients were examined. They were admitted to the series if they showed aortic incompetence in the absence of mitral stenosis and had a positive Wassermann reaction, or if they were found to have an aortic aneurism with or without a positive Wassermann reaction. The early diastolic murmur of aortic incompetence varied from soft and blowing to loud and rough, and was sometimes accompanied by a thrill. A systolic murmur was usually present as well.

The clinical signs of aneurysm were sought, but reliance was placed on radiology for its diagnosis. Care was taken to exclude the presence of rheumatic valvular disease. Auscultation to elicit a mid-diastolic murmur in the mitral area, with the addition of phonocardiography in doubtful cases, and cardioscopy during a barium swallow to exclude an enlargement of the left atrium, were the methods employed to prove the absence of mitral stenosis. Cases with doubtful dilatation of the aorta were not included. Enlargement of the left ventricle was sought, and in some cases it was surprisingly slight in the presence of long standing aortic valve disease.

Calcification of the aortic valve was looked for, especially when the systolic murmur was very rough. As only 5 of the 72 were examined at necropsy the records of the Bernhard Baron Institute of Pathology for the years 1922 to 1948 were examined to ascertain the customary pathological changes in like cases.

A history of primary luetic infection was often missing. The two common symptoms were pain in the chest and shortness of breath. Special attention was paid to pain, and having regard to its character the cases were placed in three groups. In the first there were 34 who appeared historically to have true cardiac pain; in the second there were 21 cases where the pain was somewhat atypical of cardiac pain; and in the third group 17 cases where pain was absent.

The electrocardiogram will be described in relation to these three groups (Table I). The routine leads taken were the conventional limb leads I, II, and III and chest leads CR1, CR4, and CR7. In special cases other leads were taken, and in some where the electrocardiogram was normal or nearly normal in the presence of pain, the exercise test was added. The two step test was used, and the exercise test was continued for three minutes unless pain in the chest had set in. The

electrocardiogram was then recorded immediately, and at intervals of three, five, and fifteen minutes. A positive test was assumed to be present when significant S–T depression took place. This was usually seen best in leads CR4 or CR7. The electrocardiographic findings in the three groups of cases will now be described.

TABLE I

THE ELECTROCARDIOGRAM IN 72 PATIENTS WITH SYPHILITIC HEART DISEASE

Clinical classification	Aortic incompetence	Normal cardiogram	Abnormal cardiogram					
			Ischæmic effects	L.V.P.	L.V.P. and ischæmic effects	B.B.B.	A-V conduction defect	A.F.
Cardiac pain (34)	(4) Absent	—	4	—	—	—	—	—
	(30) Present	1	15	8	6	2	—	—
Non-cardiac pain (21)	(6) Absent	5	—	—	—	—	1	—
	(15) Present	6	—	8	—	1	2	1
No pain (17)	(5) Absent	5	—	—	—	—	—	—
	(12) Present	5	—	5	—	1	—	3

Numerals indicate number of cases. Cases may appear in more than one column.
B.B.B.=Bundle-branch block.
L.V.P.=Left ventricular preponderance.
A.F.=Auricular fibrillation.

RESULTS

Ischæmic Changes. Cardiograms showing ischæmic changes were divided into two groups. The first where they predominated, and the second where they were present alongside left ventricular preponderance. In the first group were 19 cases, and in the second, 6 cases.

In the first group, abnormal Q waves were present in only two cases and Pardee sign only once, so that reliance had to be placed on S–T and T wave changes as an index of myocardial changes. Reliance was placed on a changing cardiogram, on T wave inversion atypical of left ventricular preponderance, on the lesser cardiographic changes described by Evans and McRae (1952), and on the exercise electrocardiogram.

A changing cardiogram, in the absence of other complications like arrhythmia or digitalis therapy, may be accepted as evidence of ischæmic effects. Nine cases came into this group, seven with incompetence and two without. Five cases each with aortic incompetence, showed different degrees of inversion of T waves. One showed S–T elevation and T wave inversion in leads II and III at one time, and later the T wave became upright in lead II and later still, inverted in leads II and III. Another showed left ventricular preponderance with S–T depression and T wave inversion in leads I, II, and CR7, while later the T waves moved upright in these leads (Fig. 1). Another showed transient inversion of the T waves in leads I, CR4, and CR7, and later these became upright in leads CR4 and CR7 (Fig. 2). Another showed a pattern suggestive of left ventricular

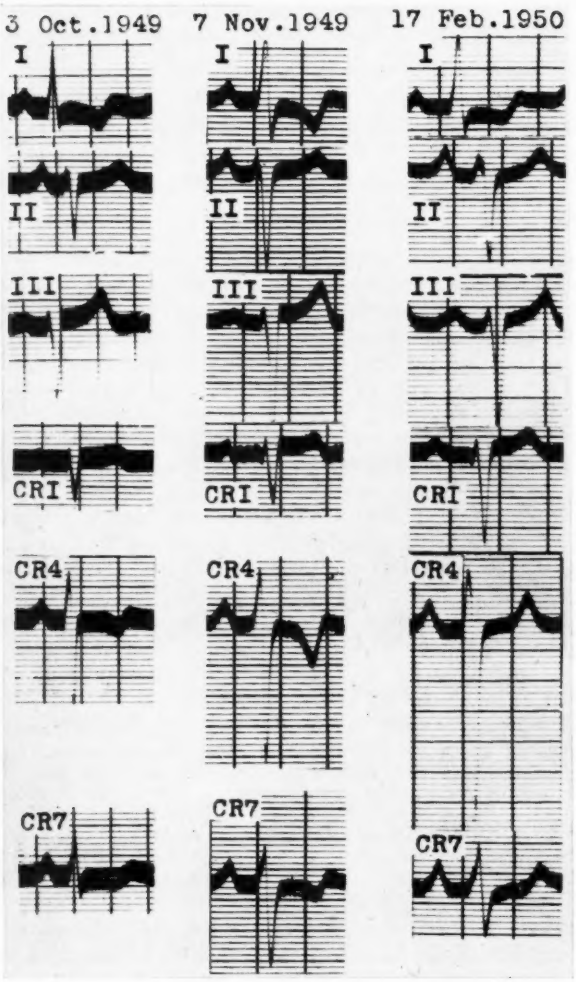


FIG. 1.—Varying inversion of T waves in lead I, CR4, and CR7.

preponderance at first, but later developed deep T wave inversion in lead CR4, deeper than in CR7, and thereafter the T waves in leads I, II, CR4, and CR7 then became flat or bifid and once more inverted.

The remaining four cases with fluctuating changes showed less deformities of the S–T segment, or flattening of the T waves. One showed transient S–T depression in leads I, CR4, and CR7. This type of change may be seen during an attack of anginal pain (Hall, 1932; Parkinson and Bedford, 1931), although this patient did not have such an attack while the tracing was being taken. The second showed low T waves in leads I and CR7, with a bifid T in CR4, which later became taller. A notch was present in the QRS in CR7 as an additional significant abnormality. The third showed a similar change, with a transient low T wave in lead I, S–T depression in CR7, and

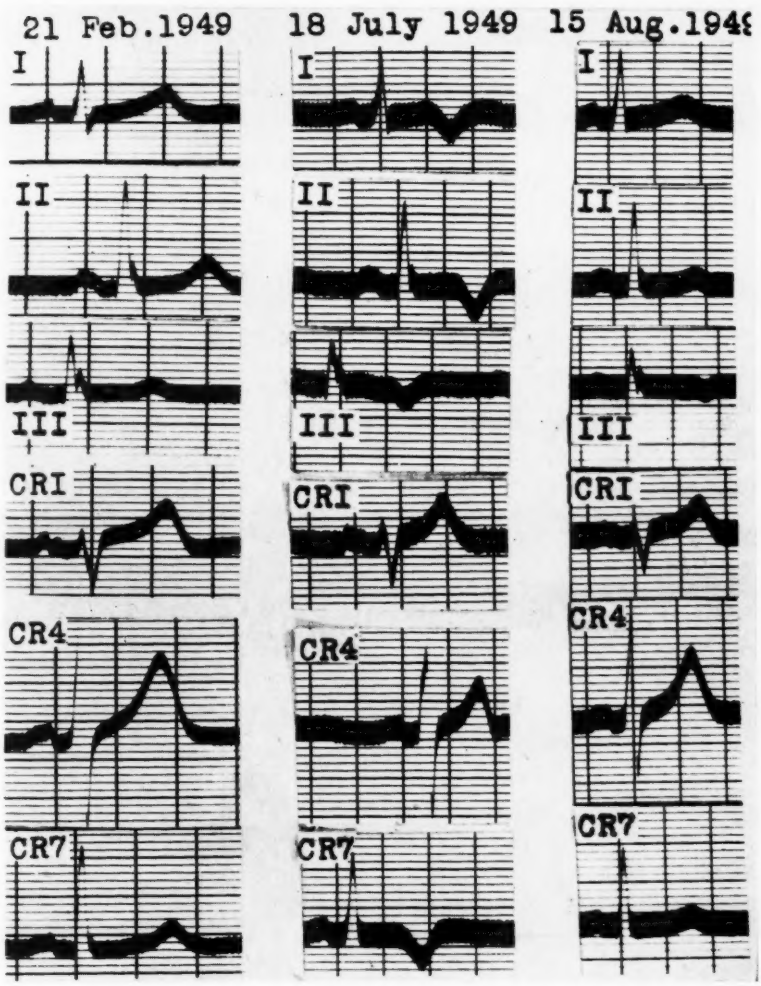


FIG. 2.—Transient inversion of T waves in leads I, II, and CR7.

a bifid T wave in CR4, and the fourth showed a flat T wave in leads I and CR7 on one occasion which later became upright. This patient died as the result of a rupture of an aortic aneurysm, and post mortem showed that the myocardial ischæmia had probably resulted from atheroma rather than obstruction of the coronary orifices by syphilitic aortitis.

T wave inversion not typical of left ventricular preponderance, usually affected leads II and III for although left ventricular preponderance of aortic valve disease may sometimes show as S–T and T wave changes in leads II, III, and CR7 (Evans, 1948), if the QRS is not tall in lead CR7 it is likely to be the outcome of a myocardial injury. Five cases showed these abnormalities. In one of these the S–T depression and T wave inversion in leads II and III suggested left ventricular preponderance, but the chest leads showed no evidence of this.

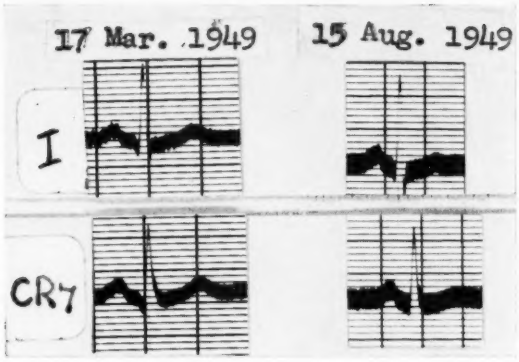


FIG. 3.—Flattening of the T waves in lead I and CR7 in the absence of aortic incompetence.

Lesser Changes. These were seen in four cases. One of these had S–T depression in leads I, CR4, and CR7, and the other S–T depression in lead I. The third showed S–T depression and flat T waves in leads I and CR7 in the absence of aortic incompetence (Fig. 3). Two of them had a positive exercise test.

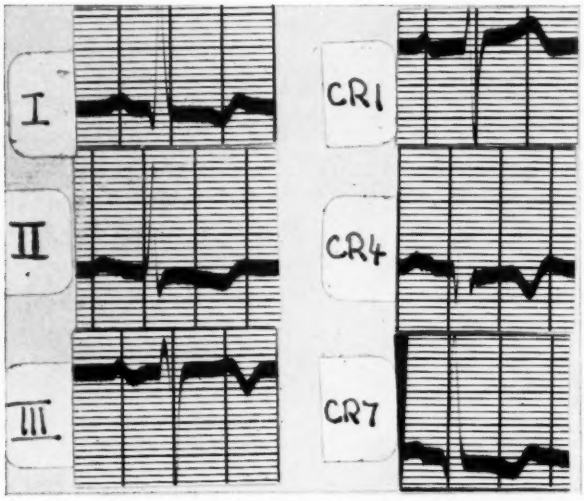


FIG. 4.—T wave inversion in lead CR4, deeper than in CR7, suggesting ischæmia.

Left Ventricular Preponderance Conjoined with Ischæmic Effects

In the presence of left ventricular preponderance, ischæmic changes are often difficult to recognize. Should the T wave in leads I or CR4 be deeper than CR7 a myocardial injury is likely to be present (Evans, 1948). Three cases showed this as a lasting feature (Fig. 4) and another as a transient sign confirming the ischæmic nature of the abnormality.

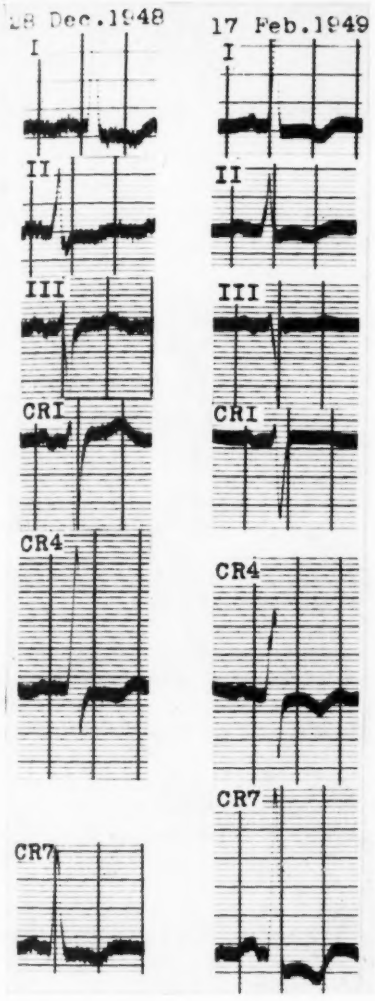


FIG. 5.—Left ventricular preponderance, but later upward bowing of the S–T segment in CR4 suggesting ischæmia.

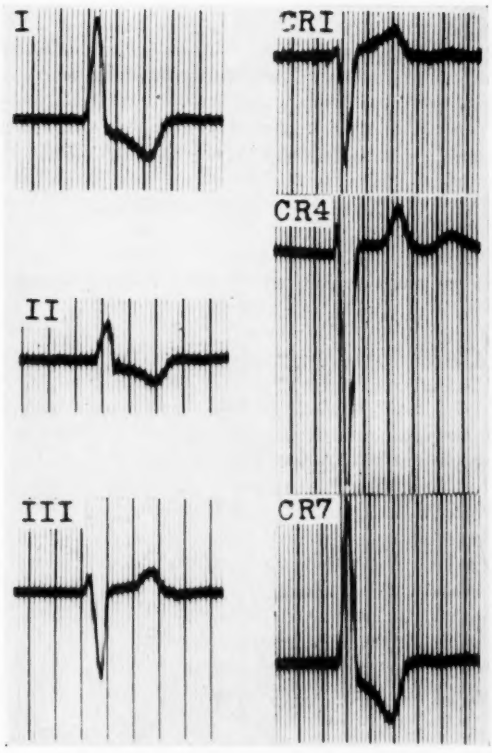


FIG. 6.—Left ventricular preponderance, but with a flattening of the S–T segment in lead CR4. Necropsy showed stenosis of the coronary orifices.

Again, alteration in the shape of the S–T segment in CR4 with upward bowing gave support to the diagnosis, and three patients showed this feature (Fig. 5). One of them died and necropsy showed great stenosis of both coronary orifices and ischæmic changes in the myocardium.

Left Ventricular Preponderance

Twenty-one cases showed this change. Twenty of them showed the usual pattern of left ventricular preponderance, namely, S–T depression and T wave inversion in leads I and CR7, but one

showed the changes in leads II, III, and CR7 and none in lead I, a pattern of left ventricular preponderance of aortic valve disease. It is well recognized that changes of left ventricular preponderance may mask ischæmic changes in the cardiogram. This is illustrated by a man, aged 66, with cardiac pain and aortic incompetence. The cardiogram showed left ventricular preponderance on four occasions, although once there was a flattening of the S–T segment in lead CR4, which might signify the presence of ischæmia (Fig. 6).

This patient died and necropsy showed considerable stenosis of the orifice of the right coronary artery from syphilitic aortitis. The myocardium of the left ventricle which was hypertrophied, showed scattered small areas of fibrosis with one larger area in the posterior wall. There was incidental moderate atheroma of the coronary arteries.

Changes in Rhythm

Four cases showed *bundle-branch block*, three of the right branch and one of the left; this last was transient and at another time showed left ventricular preponderance only.

Two patients had a *prolonged P–R period*, one of them later developing auricular fibrillation. A third patient had a *nodal rhythm*. Auricular fibrillation was seen in four, one of these had previously had a prolonged P–R period. A normal cardiogram was seen in 22 patients.

Cardiac Pain

Cardiac pain was present in 34 patients. In 30 it was induced by physical exertion especially walking, and was relieved by rest although sometimes it would occur at night and last for a time. Excitement, dreaming, and bending would sometimes precipitate attacks of pain. In the remaining four, periodic attacks of long duration as in cardiac infarction had not been associated with shorter attacks during effort.

The electrocardiogram was abnormal in 33 patients: 19 had ischæmic effects, 8 had left ventricular preponderance, 6 had left ventricular preponderance and ischæmia, and 2 had bundle-branch block. In the remaining one the tracing was normal and showed no change after exercise. This patient had typical cardiac pain 16 years previously, remained free from pain for 15 years following antiluetic treatment. This suggested that there had been a halting of the pathological process in her case.

Pain that was not accepted as anginal was present in 21 cases and in 10 of these it was thought to be unconnected with the heart condition. In eight it was related to the presence of an aneurysm, and in two it was paroxysmal, but was atypical of cardiac pain in that it was not induced by exertion. These two had nocturnal pain, particularly related to nocturnal dyspnœa and were among the eight showing left ventricular preponderance only. One of them had nocturnal pain, with left ventricular failure, but as soon as this was relieved by treatment the pain ceased. The other patient died and necropsy showed no coronary artery obstruction, confirming the wisdom of the decision to exclude such cases from the group with anginal pain. This patient experienced pain in the left shoulder for three years, unrelated to exertion but for two months before he died he complained of burning pain across the chest, coming only at night and usually related to nocturnal dyspnœa, although sometimes occurring apart from it. His cardiogram showed left ventricular preponderance with prolonged P–R interval at first, while later auricular fibrillation developed. At necropsy there was no involvement of the coronary orifices by the syphilitic aortitis nor of the arteries themselves from atheroma as shown by the injection of opaque material. The myocardium showed some small areas of patchy fibrosis involving the atria as well as the ventricles. There was no explanation for the auricular fibrillation. The presence of fibrosis was not easily explained, but might have been the result of the large size of the heart, with a relatively inadequate coronary circulation; the fibrotic stage of syphilitic myocarditis was a possible explanation, but microscopically the lesions did not suggest this. The pain appeared to be related to left ventricular failure. There were 11 patients with normal cardiograms in this group. One patient had a nodal rhythm and another a right bundle-branch block.

There were no cases with cardiographic changes indisputably the outcome of cardiac ischæmia

among 18 patients without pain. Ten had normal tracings. One had right bundle-branch block. Five had left ventricular preponderance in the presence of aortic incompetence; one of these also had auricular fibrillation. Two had auricular fibrillation without other abnormalities except the effects of digitalis.

The Changes in the Myocardium in Aortitis

To investigate the changes in the myocardium that explained the cardiographic changes, the post-mortem records of the Bernhard Baron Institute of Pathology at the London Hospital were consulted for the years 1922 to 1948. There were 180 cases of syphilitic aortitis. In 73 there was stenosis of one or both coronary orifices; 42 of these had changes in the myocardium on naked eye examination and in 31 the changes appeared to have been caused by stenosis of the coronary orifices from syphilitic aortitis, for coronary atheroma was not once severe. In fact, where the ostial stenosis from aortitis was severe, the amount of coronary atheroma was usually slight. In the remaining 11 cases showing microscopical changes in the myocardium, there were 5 with severe atheroma, one with a gumma, one with a small dilated blood space in the myocardium, and four without coronary involvement. In microscopic sections of these four there was no conspicuous evidence that the fibrosis was due to syphilitic myocarditis. The fibrosis was dense, like old scar tissue, and cells were few. It was found impossible to decide whether it was ischæmic or inflammatory.

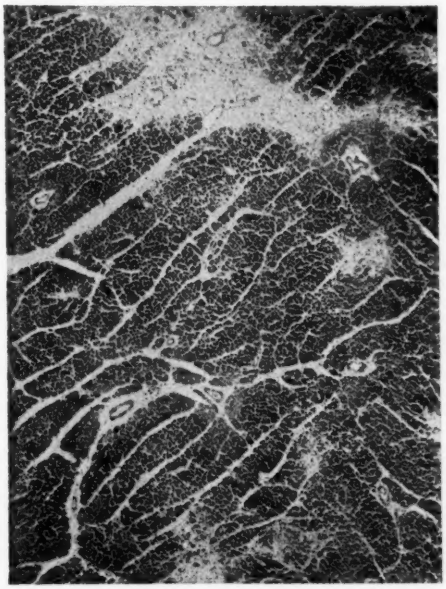


FIG. 7.—Patchy fibrosis in the myocardium (left ventricle) P.M. 47/42. H and E. Mag. ×21.

In the 31 cases myocardial fibrosis was most commonly found as small patches scattered throughout the left ventricle (Fig. 7). In some cases there were larger patches, found most frequently in the interventricular septum and in the posterior wall of the left ventricle. The papillary muscles of the mitral valve were also commonly affected. These areas of fibrosis were often subendocardial (Fig. 8) and in three they were very extensive: one involved the left half of the posterior wall, fading off in the upper part and affecting the whole circumference at the apex; in another an area of fibrosis about 0·2 cm. thick involved the whole

FIG. 8.—Subendocardial fibrosis in the wall of the left ventricle. Van Gieson. Mag. × 19.

subendocardial region of the left ventricle, and was most severe in the posterior wall and posterior part of the interventricular septum: in a third case there was a very thin area of subendocardial fibrosis in the posterior papillary muscles of the mitral valve. The large size of these areas suggest that they might represent the fibrotic stage of formerly acute cardiac infarction, but between the fibrosis and the normal subpericardial muscle there were areas of muscle fibres with poorly staining nuclei suggesting slow degeneration, and some multinucleate muscle fibres suggesting regeneration.

These features indicate a gradual ischæmic atrophy rather than the fibrotic stage of acute infarction. In one case there was a large area of necrosis; this, though somewhat patchy and ill-defined, involved an area that measured 12 × 9 cm. in the anterior part of the interventricular septum. From its microscopical appearance the infarction was judged to be three to four days old. In the region of this recent infarction there was also slight evidence of old ischæmic atrophy in the form of a few small areas of fibrosis and vacuolation of the muscle fibres immediately under the endocardium. In another case there was a small recent infarct in the posterior wall of the left ventricle. In yet another there were very small areas of recent infarction related to areas of ischæmic atrophy.

Thus, there were three main effects of cardiac ischæmia from luetic stenosis of the coronary orifices. First, small patches of fibrosis scattered throughout the left ventricle probably the result of gradual ischæmia and rarely associated with small areas of recent infarction: this was the commonest change. Secondly, there were large areas of subendocardial fibrosis, either the result of recent infarction or more likely of gradual ischæmia. Thirdly, and rarely, large areas of recent infarction were present.

DISCUSSION

The findings in this series regarding the relation of cardiac pain and the cardiogram are at variance with those of other authors (Smith and Blackford, 1938; Burch and Winsor, 1942). Thus, in this series 33 out of 34 cases with cardiac pain showed abnormal tracings, whereas only 17 out of 38 were abnormal among those with no pain or non-cardiac pain in the chest. This may be due to difference in criteria of normality or to the use of an increased number of chest leads, but may also be due to the fact that previous writers have not differentiated cardiac pain from non-cardiac

pain. Even so, there is a difference between the findings in those with pain in the chest of any sort (42 out of 54 abnormal) and those with no pain (8 out of 18 abnormal). Nevertheless, although the cardiogram is abnormal in a high percentage of cases with cardiac pain, positive evidence of cardiac ischæmia is often difficult to obtain; this is attributable first to the rarity of abnormal Q waves in the tracings (only 2 cases in this series) and secondly to the frequent presence of left ventricular preponderance from aortic incompetence.

The rarity of large areas of infarction post mortem in syphilitic heart disease, as noted by previous authors (Burch and Winsor, 1942; Cole and Bohring, 1944), is confirmed in this series: only one example among 180 cases of syphilitic heart disease was found on critical examination of the post-mortem records.

The presence of S–T depression indicating lesser myocardial changes may be difficult to distinguish in the presence of left ventricular preponderance on a single tracing. The shape of the S–T and T waves, regarded by Parsonnet and Bernstein (1943) as important, is not always reliable, but a changeability of the tracing may be a valuable aid to diagnosis if other factors that cause alteration in the cardiogram can be ruled out. Thus, nine cases in this series showed this changeable cardiogram. None of these had heart failure, none gave a history of paroxysmal tachycardia, and none was receiving digitalis or arsenic; one was taking penicillin, while others were having iodine and mercury or bismuth. There did not seem to be any evidence to incriminate these drugs.

Katz (1946) has noted the changing cardiogram in syphilitic heart disease relating it to transient coronary insufficiency, using Masters terminology. The electrocardiographic and pathological findings in this series may be similar to those described by Master *et al.* (1944) as characteristic of coronary insufficiency. The variation in the cardiogram and the absence of Q waves have been noted, and the pathological findings appear to be similar. The subendocardial region and the papillary muscles are mainly affected and the lesions are often of a patchy distribution: it is probable that these changes are due to slow ischæmia and to more abrupt episodes. Both types of lesion were found in this series and have been described by Love and Warner (1934) and Norris (1937).

The subendocardial localization of the lesions is attributed to the factors already discussed and left ventricular hypertrophy, being commonly present in syphilitic heart disease, is likely to be of particular importance. The S–T depression in the chest leads CR4–7 of the cardiogram are features both of left ventricular hypertrophy and of subendocardial ischæmia, and the presence of one may obscure the other.

The cases with cardiac pain and slight abnormalities in the cardiogram were investigated by the exercise test. Two of these gave positive tests and further experience may extend the use of this test, particularly if it can reveal ischæmia when the tracing already shows left ventricular preponderance. Bundle-branch block indicates myocardial changes if it involves the left branch and when there is only moderate aortic incompetence.

Auricular fibrillation has been said to be rare in syphilitic heart disease (Willius, 1930; Brenner, 1933), and in this series there were only four cases: one of them post mortem had no change other than syphilitic heart disease to account for the abnormal rhythm. In the other three the heart rate was slow and the patients were elderly. These features suggest that they were examples of lone fibrillation (Evans and Swann, 1954), rather than due to syphilitic heart disease. A-V dissociation has been reported in most series apart from gumma of the heart. A prolonged P–R interval in two cases was the only evidence in the present series of A-V conduction defect, and one patient had nodal rhythm.

Summary

The cardiograms of 72 cases of syphilitic heart disease were examined and the findings compared with those published by other authors.

The cardiograms were abnormal in 50 out of 72 patients and this was almost invariable in patients with cardiac pain (33 out of 34 cases).

Ischæmic changes are difficult to tell in the presence of left ventricular preponderance. The

position of the fibrosis in the subendocardial region of the posterior wall of the left ventricle and in the interventricular septum adds another difficulty to the diagnosis of ischæmic changes in the cardiogram. A changing cardiogram was often the best evidence of ischæmia and was seen in 9 cases. Auricular fibrillation may result from syphilitic heart disease, although it is rare.

The presence of a large area of cardiac infarction was rare, and the changes in the myocardium usually indicated the presence of a more tardy process of limited extent in the form of ischæmic atrophy with replacement fibrosis, sometimes associated with small areas of recent necrosis. Such changes produce T wave inversion in the electrocardiogram without Q waves as a rule.

When syphilitic aortitis has been discovered or suspected the examination is incomplete if it does not include a cardiogram, for this often tells of involvement of the orifices of the coronary arteries by aortitis.

I wish to thank Dr. William Evans—physician to the department—for his advice and criticism, and I am grateful to Dr. W. Woods and Dr. J. F. Smith of the Bernhart-Baron Institute of Pathology for their advice on the pathological material.

References

Annett, J. H. (1928). *Amer. J. med. Sci.*, **176**, 65.
Berk, L. H. (1941). *N.Y. State J. Med.*, **41**, 223.
Brenner, O. (1933). *Birm. med. Rev.*, **8**, 161.
Bruenn, H. G. (1934). *Amer. Heart J.*, **9**, 421.
Burch, G. E., and Winsor, T. (1942). *Amer. Heart J.*, **24**, 740.
Chamberlain, E. N., and Follows, J. (1933). *Quart. J. Med.*, **2**, 221.
Cole, S. L., and Bohring, A. (1944). *Amer. J. med. Sci.*, **207**, 317.
Cocmbs, C. F. (1932). *Quart. J. Med.*, **25**, 179.
Evans, W. (1948). *Cardiology*. Butterworth, London.
——, and McRae, C. (1952). *Brit. Heart J.*, **14**, 42.
——, and Swann, P. (1954). *Brit. Heart J.*, **16**, 189.
Gallavardin, L. (1932). *J. Méd. Lyon.*, 549.
Hall, D. (1932). *Lancet*, **1**, 1254.
Heimann, H. L. (1927). *Brit. med. J.*, **1**, 133.
Ingraham, R., and Maynard, E. P. (1930). *Amer. Heart J.*, **6**, 82.
Jones, E., and Bedford, D. E. (1943). *Brit. Heart J.*, **5**, 107.
Juster, I. R. Pardee, H. E. B. (1929). *Amer. Heart J.*, **5**, 84.
Katz, L. N. (1946). *Electrocardiography*. 2nd ed., London, p. 435.
Kletz, S. D., and Crede, R. H. (1945). *Amer. Heart J.*, **30**, 551.
Love, W. S., and Warner, G. C. (1934). *Amer. J. Syph.*, **16**, 154.
Levine, H. D., and Ford, R. V. (1950). *Circulation*, **1**, 246.
Master, A. M., Jaffe, H. L., Dack, S., and Grishman, A. (1944). *Amer. Heart J.*, **27**, 803.
Norris, J. C. (1937). *J. Amer. med. Ass.*, **108**, 169.
Parkinson, J., and Bedford, D. E. (1931). *Lancet*, **1**, 15.
Parsonnet, A. E., and Bernstein, A. (1943). *Unolog. Cut. Rev.*, **47**, 516.
Smith, C., and Blackford, L. M. (1938). *Amer. J. Syph.*, **22**, 168.
Sprague, H. B. (1942). *J. Mt. Sinai Hosp.*, **8**, 1034.
Turner, K. B., and White, P. D. (1927). *Arch. intern. Med.*, **39**, 1.
Willius, F. A. (1930). *Amer. Heart J.*, **6**, 113.
Yu, P. N. G., and Stewart, J. (1950). *Amer. Heart J.*, **39**, 862.

THE ELECTROCARDIOGRAM IN PECTUS EXCAVATUM

BY

JORGE MARTINS DE OLIVEIRA, MOHINDER P. SAMBHI, AND HENRY A. ZIMMERMAN

From St. Vincent Charity Hospital, Cleveland, Ohio, U.S.A.

Received December 11, 1957

Pectus excavatum is a deformity of the chest that consists of backward displacement of the sternum and costal cartilages giving rise to a depression in the xiphisternal area. This malformation may appear isolated or associated with other anomalies. The occurrence of pectus excavatum with congenital heart disease has been reported by several observers (Evans, 1946; and McKusick, 1955). Embarrassment of circulation amounting to heart failure has also been described (Ravitch, 1951). Even in the absence of any cardiac condition, electrocardiographic changes are to be expected, because of alterations in the position of the heart. Whether these changes occur as a consequence of cardiac rotation only or also on account of compression of the heart by the chest cage has not yet been established. However, the recent advances in electrocardiography based on vectorial concepts allow us to consider that in cases of pectus excavatum, in the absence of associated cardiac disease, the modifications in the position of the heart are the most important factors, so far as the electrocardiographic changes are concerned.

Previous reports on the electrocardiogram in this malformation exist. Dressler and Roesler (1950) in 10 of their 13 cases, reported inversion and notching of the T waves in præcordial leads (from V1 to V4) as the most remarkable findings. Although most patients in their series were adults, we are not sure that these T wave changes can be considered strictly pathological, since in our experience we have noticed that many normal women retain the juvenile T wave pattern through adult life.

Wachtel *et al.* (1956), studying 13 other cases, described the changes in QRS complex in lead V1 as the most important finding in pectus excavatum: in eight of these patients, an rsr′ pattern was observed. The authors stressed that the above pattern does not indicate disturbance in conduction, but is the consequence of cardiac rotation. They further emphasized the fact that the anatomical configuration of the chest in this malformation, making the correct application of the præcordial lead electrodes difficult, does not permit an exact evaluation of the T wave changes.

ANALYSIS

Our present study is based on 13 patients with pectus excavatum in whom no evidence of heart disease was found. The ages varied from 5 to 75 years, the average being 24 years. Eight out of these were male and the remaining five were female. Twelve classical leads were recorded in all patients, and in two of them intracavitary electrocardiograms have also been studied. For the sake of convenience, we have divided our analysis into the following three parts.

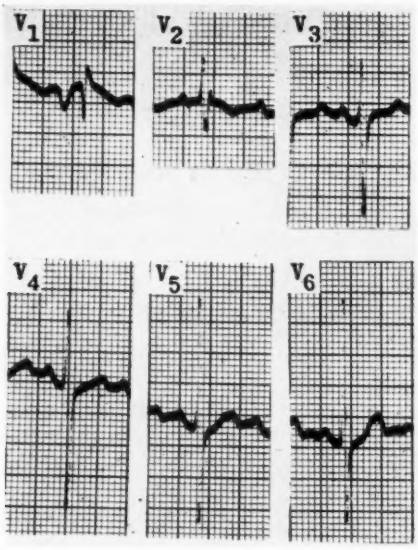


FIG. 1.—Entirely negative P wave in lead V1.

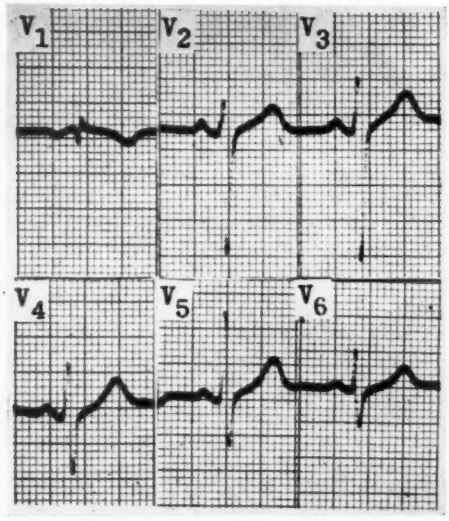


FIG. 2.—qr pattern in V1; disproportional amplitude of the QRS complex in this lead, as compared to V2.

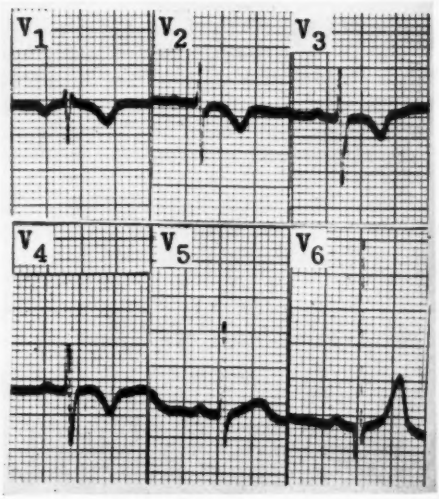


FIG. 3.—rsr′ pattern in V1; it was present in 8 out of our 13 cases.

1. *Auricular Activation.* The auricular vector was localized between −25° and +75° in the frontal plane, with a backward orientation in the horizontal plane in all the cases.

P wave. The duration of this wave in the limb leads was within normal limits in 11 patients; in the remaining two, it exceeded 0·10 seconds. In 11 out of our 13 cases (Fig. 1) the P wave was entirely negative in lead V1. In the other two cases, although biphasic, it was predominantly negative. Such an entirely negative P wave in lead V1 is an infrequent finding, even in the presence of marked left auricular hypertrophy or dilatation. In these 11 patients, this pattern of the P wave in the first præcordial lead resembled exactly the one seen in aVR. The reason for this pattern in patients with pectus excavatum will be discussed later.

P–R interval. This was within normal limits in all cases. We did not meet any arrhythmias in our patients with pectus excavatum, as has been reported by other observers (Schaub, and Wegmann, 1954).

2. *Ventricular Activation.* The duration of the QRS complex was within normal limits in all

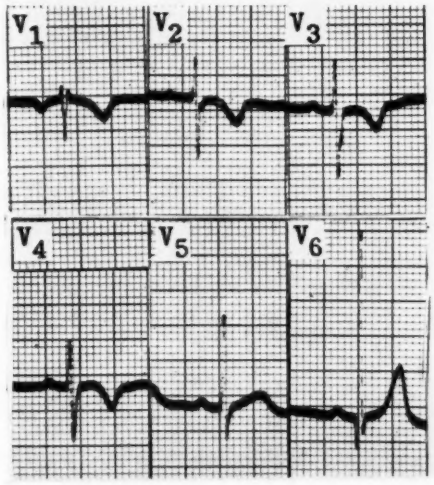


FIG. 4.—Negative T waves from V1 to V4 in a 5-year-old female with pectus excavatum (same case as Fig. 3).

patients. The lead V1 exhibited a qr pattern in four of the cases (Fig. 2) an rsr′ pattern in eight (Fig. 3) and a normal rS pattern in the remaining one.

In lead V2 the pattern of QRS complex was normal in eight patients, but in the other five, the rsr′ pattern was present. It seems important to note that the cases which exhibited a Q wave in V1 also presented a disproportionally small total amplitude of the QRS complex in this lead, as compared to V2 (Fig. 2). Such a phenomenon has also been observed frequently in patients with enlarged right auricle. In the limb leads, in all of our cases an S_1S_3 or S_1Q_3 pattern, characterizing a clockwise rotation of the heart, was seen.

$\widehat{SA}QRS$. It varied between −100° and +110° in the frontal plane, with a backward orientation in the horizontal plane in all cases. The electrical axis deviated to the right in six patients (46%), to the left in one (8%), and was within normal limits in the remaining six (46%).

3. Ventricular Repolarization. Table I summarizes the pattern of T waves in the præcordial leads in our patients.

TABLE I.—Pattern of the T waves in 13 patients with funnel chest.

CASE NO.	MORPHOLOGY OF THE T WAVES IN PRECORDIAL LEADS					
	V1	V2	V3	V4	V5	V6
1	-	+	+	+	+	+
2	-	-	-	-	+	+
3	-	+	+	+	+	+
4	-	+	+	+	+	+
5	-	-	±	+	+	+
6	-	+	+	+	+	+
7	-	+	+	+	+	+
8	-	+	+	+	+	+
9	-	+	+	+	+	+
10	-	-	+	+	+	+
11	-	+	+	+	+	+
12	-	+	+	+	+	+
13	-	-	+	+	+	+

(+) positive (−) negative

It is evident from Table I that in all cases the T wave was negative in lead V1; in four it also appeared negative in V2, and in only one patient did this negativity extend up to V4. We should point out, however, that this last patient was a five-year-old girl. Our findings do not agree with those of some other authors (Dressler, and Roesler, 1950) who reported negative T waves up to V3 in the majority of their adult patients. As we have emphasized before, we do not think that negative T waves in right præcordial leads have any special meaning as far as pectus excavatum is concerned. However, in those cases in whom there is compression of the right cardiac chambers by the thoracic deformity, as has been reported by Sweet (1944), an explanation for the negativity of T waves in right præcordial leads can be suggested. We think that in such cases the mechanical injury thus affecting the epicardium may produce a delay in the initiation of the repolarization in this region. Consequently, the recovery process starts in the subendocardial portions and the orientation of the T vector is reversed (Fig. 5).

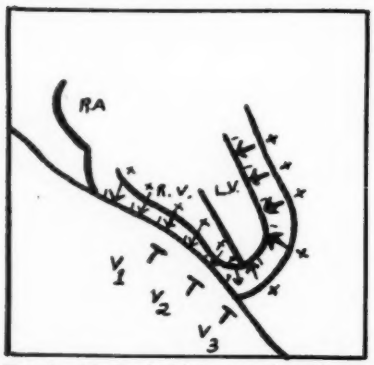


FIG. 5.—Mechanical injury produced by the thoracic deformity causing reversed repolarization.

Dressler and Roesler (1950) reported a case of pectus excavatum who suffered from typical attacks of angina pectoris and whose electrocardiogram showed negative T waves in multiple præcordial leads. In our own experience, as far as the T waves in patients with pectus excavatum

are concerned, the only finding of any statistical significance is the negativity of this wave in lead V1 (all our cases). However, this is not an infrequent finding in normal subjects. The mean vector of ventricular repolarization varied between 0° and +65° in the frontal plane, while a forward orientation in nine cases, and a backward orientation in four was found in the horizontal plane.

Discussion

Two findings in the electrocardiogram in our cases of pectus excavatum deserve special attention, on account of the constancy with which they appeared: the pattern of the QRS complex in lead V1 and the spatial orientation of the mean auricular activation vector. Wachtel *et al.* (1956) and Schaub and Wegmann (1954) also have pointed out that in their series, the rsr′ pattern was a frequent finding. In a previous communication (Martins de Oliveira and Zimmerman, 1958) we have emphasized that this pattern does not necessarily mean disturbance in conduction in the right branch of the bundle of His itself. It is an established fact (Penaloza and Tranchesi, 1955) that the r′ wave in the first præcordial lead signifies the depolarization of the basal portion of the right ventricle as well as the higher parts of the interventricular septum, and further, that it is present whenever the mean activation vector of these regions is oriented forward and to the right, either as a consequence of hypertrophy and dilatation of these basal portions or because of a marked rotation of the heart.

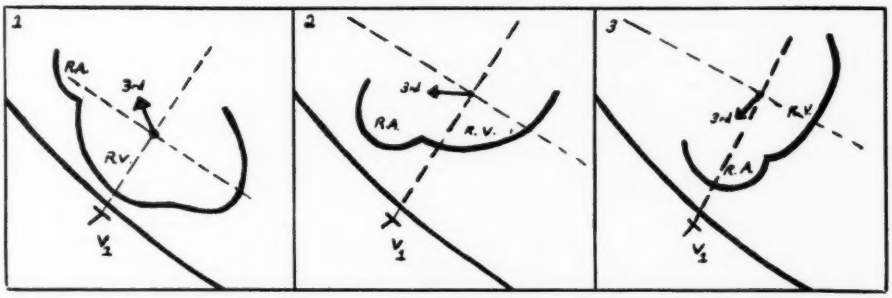


Fig. 6.—Rotation in the position of the heart: (1) Normal position. (2) Backward rotation of the ventricles—the basal (3rd) vector is now oriented to the positive side of V1 which explains the r′ wave in this lead. (3) Backward rotation of the ventricles and anterior displacement of right auricle—lead V1 now reflects the intracavitary potentials.

The qr pattern in lead V1, as has been stressed by Sodi-Pallares and Calder (1956) represents the transmission of the electrical effects arising from the basal parts of the interventricular septum to the right præcordial leads through an enlarged right auricle. In other words, the right auricular chamber, being situated exactly underneath the exploratory electrode of V1 would permit the direct transmission of intracavitary potentials to that lead.

In cases of pectus excavatum, as a consequence of the thoracic deformity itself, no enlargement would be expected, either of the right auricle or of the basal portions of the right ventricle, as long as no circulatory embarrassment is present. However, a rotation of the heart seems quite evident in these cases. Such a rotation, depending on its degree, may explain the appearance of both rsr′ and qr patterns in lead V1 in patients with pectus excavatum. In those cases in which there is only a slight rotation, not enough to bring the right auricle to such an anterior position so as to be immediately beneath lead V1, the presence of an r′ wave may be explained by the rightward and forward deviation of the mean depolarization vector of the basal ventricular portions. On the other hand, cases where the right auricle assumes the position directly below the exploring electrode of V1, as a consequence of a greater rotation of the heart, this lead now reflects the auricular

intracavitary potentials and a qr pattern appears (Fig. 6). The simultaneous recording of V1 and of the right auricular cavity obtained in two of our cases, showing the striking similarity of the two tracings, is a strong evidence of this (Fig. 7).

In all our patients, the auricular vector was oriented backwards so producing a negative P wave in lead V1. In spite of the fact that this point has not been considered by other authors (Dressler and Roesler, 1950; Wachtel *et al.*, 1956; Schaub and Wegmann, 1954) the inspection of the records published in their series demonstrates the constant presence of this finding. In our opinion, the

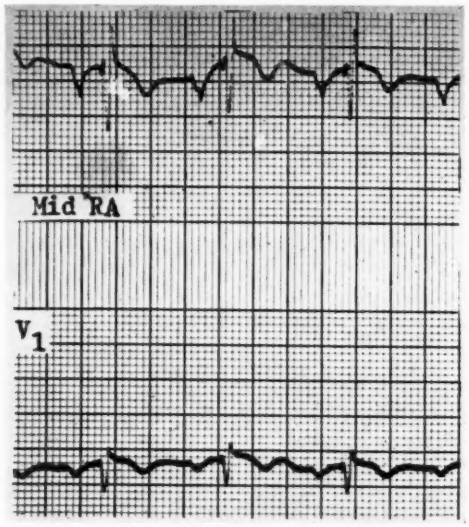


Fig. 7.—Simultaneous recording of V1 and right auricular cavity in a patient with pectus excavatum. Notice the similarity of the two tracings.

rotation of the heart that had produced these changes in the pattern of the qrs complex seems also to be responsible for this alteration in the orientation of the auricular vector. We further feel that the more anterior situation of the right auricle is the reason for finding P waves in lead V1 very similar to those observed in right auricular intracavitary records.

We are not sure whether the degree of cardiac rotation in cases of pectus excavatum is proportional to the intensity of the thoracic deformity; or if other factors, such as the body build of the patients, are also involved.

Evidently, the electrocardiogram is not an important factor in the primary diagnosis of funnel chest, since this can be established by simple inspection of the thorax. However, as the electrocardiographic changes in this deformity often resemble those seen in certain cardiopathies, as for instance mitral stenosis with pulmonary hypertension (Pruitt and Robinson, 1956) or atrial septal defect (Monroy and Cabrera, 1952), it becomes important to recognize the existence of this chest anomaly in order to avoid a misdiagnosis. Further, the analysis of the electrocardiogram in these cases offers an excellent opportunity to appreciate certain interesting consequences of cardiac rotation.

1. Our observation in two cases faitfully confirmed the experience of other authors (Sodi-Pallares and Calder, 1956; Kossman *et al.*, 1950) regarding the transmission of intracavitary potentials to lead V1, whenever the right atrial chamber is directly below the exploratory electrode.

2. The presence of a disproportion between the amplitudes of the QRS complex in V1 (small) and V2 (large) is also an argument in favour of the fact that the right auricle is situated immediately below the electrode of V1, since transmitted intracavitary forces obviously will not have the same amplitude as compared to the direct ones from the epicardial surface of the ventricle, as exhibited in V2 and the rest of the præcordial leads.

3. The frequent appearance of an rsr′ pattern in V1 in patients with pectus excavatum gives us a further opportunity to recapitulate an important conclusion that we (Martins de Oliveira and Zimmerman, 1958; and Walker *et al.*, 1956) have stressed before: this pattern does not mean, at least as a rule, a block in the right branch of the bundle of His itself but is the manifestation of vectorial forces transmitted to this præcordial lead, either as an expression of dilatation and hypertrophy of the basal ventricular regions or simply as a result of the rotation of the heart, as it happened in the cases of this present study.

Conclusions

The change in cardiac position caused by the thoracic deformity in patients with pectus excavatum produces more or less constant characteristic electrocardiographic findings, which, although not pathognomonic, yet can be suggestive of this anomaly.

These findings consist of: (*a*) S_1S_3 or S_1Q_3; (*b*) negative P waves in V1; and (*c*) qr or rsr′ in VI.

We think these findings are chiefly related to clockwise rotation of the heart on its longitudinal axis, backward orientation of the auricular vector, and transmission of intracavitary potentials to the right præcordial leads.

These electrocardiographic changes, which, for different reasons, can be seen in other conditions like atrial septal defect or mitral stenosis with pulmonary hypertension, may lead to erroneous diagnosis if the electrocardiogram is analysed without previous knowledge of the existence of such thoracic deformity.

The authors gratefully acknowledge the technical assistance of Miss Helen Kleinhenz, R.N., Mrs. Marjorie McIntyre, R.N., and Miss Donna Wolfram.

References

Dressler, W., and Roesler, H. (1950). *Amer. Heart J.*, **40**, 877.
Evans, W. (1946). *Brit. Heart J.*, **8**, 162.
Kossman, C. E., Berger, A. R., Rader, B., Brumlik, J., Briller, S. A., and Donnelly, J. H. (1950). *Circulation*, **2**, 10.
Martins de Oliveira, J., and Zimmerman, H. A. (1958). *Amer. Heart J.* **55**, 369.
Monroy, J. R., and Cabrera, E (1952). *Arch. Inst. Cardiol. Mexico*, **22**, 330.
McKusick, V. A. (1955). *Circulation*, **11**, 321.
Penaloza, D., and Tranchesi, J. (1955). *Amer. Heart J.*, **49**, 51.
Pruitt, R. D., and Robinson, J. G. (1956). *Amer. Heart J.*, **52**, 880.
Ravitch, M. M. (1951). *Surgery*, **30**, 178.
Schaub, F., and Wegmann, T. (1954). *Cardiologia*, **24**, 39.
Sodi-Pallares, D., and Calder, R. M. (1956). *New Bases of Electrocardiography*, 1st English ed. translated from 3rd Spanish ed. The C. V. Mosby Company.
Sweet, R. H. (1944). *Ann. Surg.*, **119**, 922.
Wachtel, F. W., Ravitch, M. M., and Grishman, A. (1956). *Amer. Heart J.*, **52**, 121.
Walker, J. W., Mattingly, T. W., Pollock, B. E., Carmichael, D. B., Inmon, T. W., and Forrester, R. H. (1956). *Amer. Heart J.*, **52**, 547.

MODIFICATION OF VENTRICULAR GALLOP RHYTHM INDUCED BY POOLING OF BLOOD IN THE EXTREMITIES

BY

JAMES J. LEONARD, ARNOLD M. WEISSLER, AND JAMES V. WARREN

*From the Department of Medicine, Duke University School of Medicine, Durham, North Carolina**

Received November 7, 1957.

Ventricular gallop is a low-pitched early diastolic sound occurring at the termination of the rapid phase of ventricular filling, it is commonly encountered clinically as a sign of incipient or actual congestive heart failure. Since this sound appears to be related to the dynamics of diastolic ventricular inflow, it was felt that additional information regarding its genesis might be obtained from a study of the effects of peripheral pooling of blood. In normal subjects tourniquet pooling of blood has been extensively studied and has been shown to produce appreciable pressure and flow alterations within the heart. The present report deals with the effects of such a procedure in 18 patients with ventricular gallop rhythm.

Materials and Methods

Eighteen patients in hospital were studied. The majority had hypertensive cardiovascular disease or idiopathic myocardial failure. Although most had previously had evidences of cardiac failure, they were, at the time of the study, either compensated or displaying minimal evidence of failure. Only patients with gallop sounds that were readily audible and phonocardiograms free from extraneous respiratory sounds or interfering cardiac murmurs were utilized. Because the patients were studied while they were lying quietly on a flat comfortable surface, those who were dyspnœic, restless, or orthopnœic could not be satisfactorily investigated. Since the purpose of the cuffs was to trap blood in the extremities, patients with peripheral œdema were not included. If phonocardiograms or apex tracings gave evidence that the sound represented partial or complete summation with an atrial gallop sound or the præcordial atrial wave, it was discarded.

All sound tracings were taken on the logarithmic scale with the Sanborn Twinbeam photographic recording instrument at a paper speed of 75 mm./sec. The standard 50-mm. open bell chest piece was placed on the chest wherever the sounds to be investigated were best demonstrated. This was usually at the apex. In many instances additional tracings were taken to record the linear or apex cardiogram utilizing a piezo-electric crystal microphone. These vibrations were recorded simultaneously with and from the same chest piece as the logarithmic phonocardiograms.

In order to study the effect of peripheral blood pooling, pneumatic cuffs were placed around all extremities. Care was taken to apply the cuffs as high as possible without causing discomfort. The cuffs were inflated simultaneously and rapidly to the diastolic blood pressure, or 100 mm. of mercury in those with severe diastolic hypertension. Inflation was sustained for five minutes and the cuffs suddenly released. Following control sound tracings, recordings were made at minute intervals during the period of inflation. The period during cuff release and one minute thereafter was also recorded.

* This research was supported in part by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command under contract No. AF18(600)1542, and by a research fellowship (Dr. Weissler) from the American Heart Association, and by a research grant (H–1217), and a Traineeship (Dr. Leonard) from the National Heart Institute, National Institutes of Health, Public Health Service.

Results

Control phonocardiograms showed the ventricular gallop deflections usually 2–3 cycles in duration, occurring 0·14 to 0·24 second after the onset of the second sound (Fig. 1). The apex cardiograms demonstrated large, steep, pointed, filling waves, the peaks of which were simultaneous with the gallop sound (Fig. 2). In many instances these waves represented the most prominent excursion of the chest wall during the cardiac cycle.

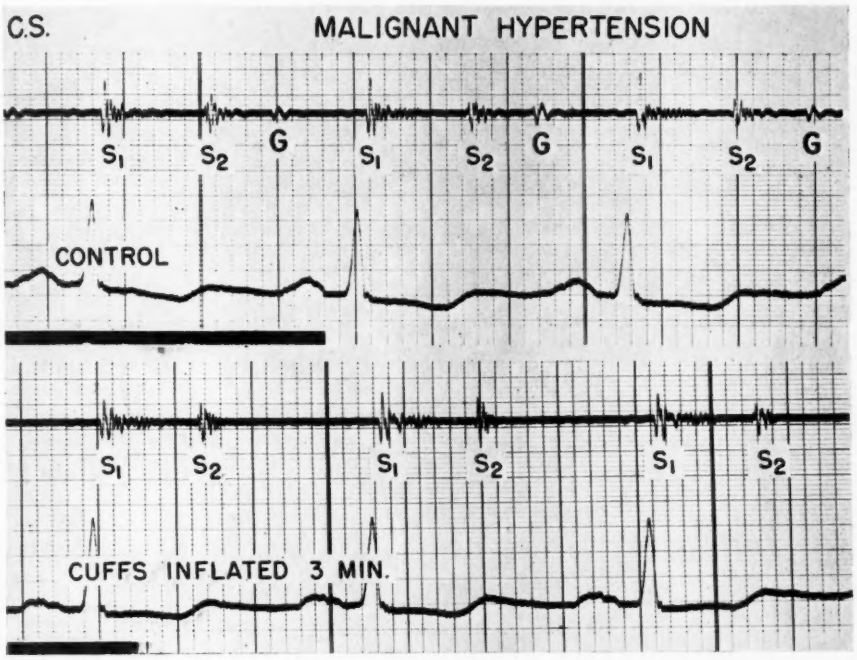


FIG. 1.—Simultaneous electrocardiograms and logarithmic phonocardiograms taken from a patient with a prominent ventricular gallop (G). The lower tracing taken three minutes after inflation of venous occlusive cuffs shows the gallop to have disappeared.

With cuff inflation in eight cases (44% of entire group studied) the gallop sound progressively decreased in intensity until it completely disappeared (Fig. 1). In two others (11%) there was a striking decrease in the amplitude of the sound, but it was still visible on the tracings obtained during the fifth minute of inflation.

Accompanying these changes there was a similar and concurrent decrease in the amplitude of the apex cardiogram, the sharply spiked wave being replaced by a more gently sloped filling curve (Fig. 2). While the cuffs were inflated, no significant changes in the pulse rate or intensity of the second heart sound were noted.

The first sound increased with cuff inflation in two cases. Both were patients with severe hypertension and prominent atrial sounds in addition to the ventricular gallop. Such an increase in the first heart sound occurs frequently after blood pooling in patients with atrial gallop rhythm (Leonard *et al.*, 1957).

A few cycles after release of cuffs the gallop sound and præcordial wave returned. The magnitude of both then frequently exceeded their initial amplitude for the next 10–20 beats before

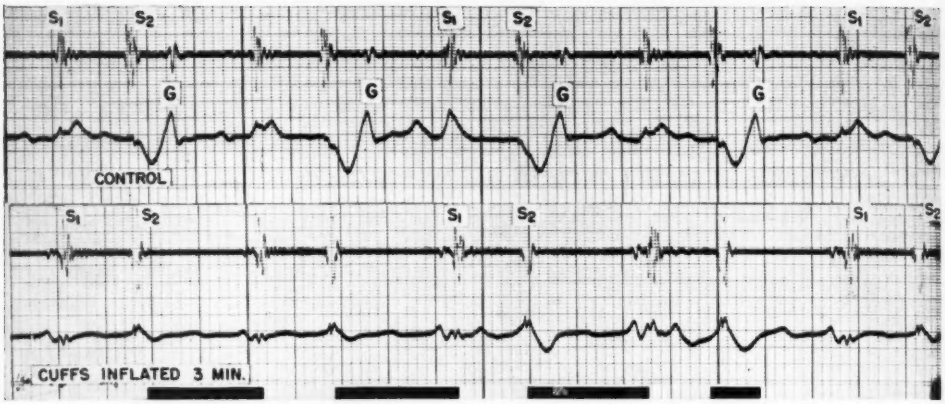


FIG. 2.—Simultaneous logarithmic phonocardiogram and apex cardiogram taken from a patient with a loud ventricular gallop (G). Note the steep pointed diastolic wave, the peak of which is synchronous with the gallop sound. The lower tracing was recorded after venous cuffs had been inflated for 3 minutes. The gallop sound has disappeared and the large peaked diastolic wave of the apex cardiogram has become shallow with more gradual slope.

returning to the control level. In some instances, as the peak of apex cardiograms became steeper, it moved closer to the second heart sound (Fig. 3). The gallop sound also occurred earlier and appeared to be sharper and higher pitched.

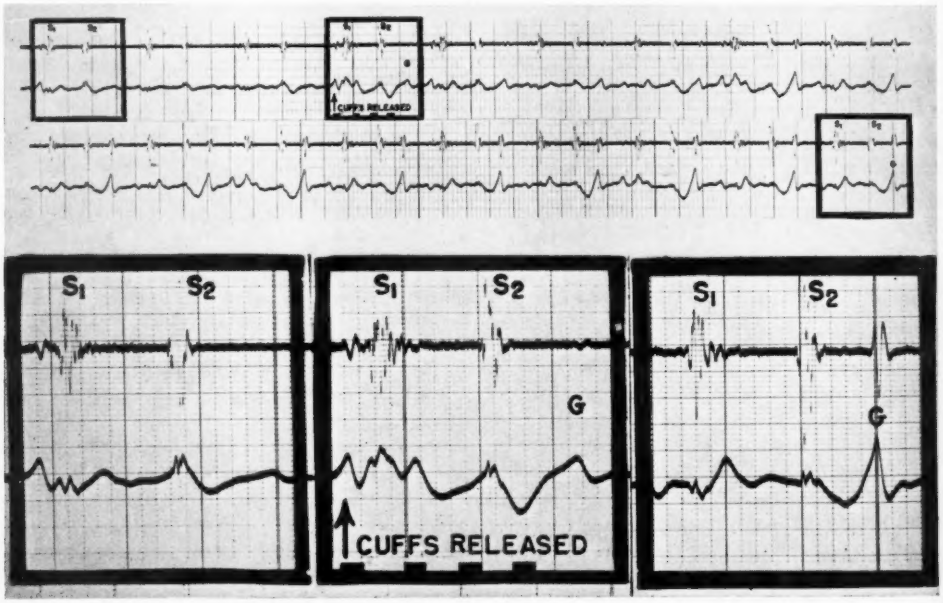


FIG. 3.—Simultaneous logarithmic phonocardiogram and apex cardiogram. Upon release of venous occlusive cuffs the diastolic filling wave of the apex cardiogram becomes larger, steeper, and its peak occurs earlier. The gallop sound (G) which has returned upon release of cuffs occurs simultaneously with the peak of this diastolic wave. As the peak of the wave becomes steeper and occurs progressively closer to the second heart sound, similar changes occur in the timing of the gallop sound.

Discussion

The patients observed in this study have recorded diastolic sounds satisfying the criteria for a ventricular (protodiastolic, rapid ventricular filling) gallop (Wolferth and Margolies, 1933). All were patients with serious cardiovascular disease and most had evidence of congestive heart failure. From an acoustic and probably mechanical standpoint, the sound recorded is essentially the same as the physiological third heart sound (Dock *et al.*, 1955). It differs in that it is now associated with a failing heart, the relationships to other vascular phenomena being exactly the same. It is of note that pathological gallop sounds are usually accompanied by a much more prominent apical impulse than the physiological third sound. The apex cardiogram, as well as the audible sound, is altered by blood pooling.

Tourniquets applied in the fashion used in this study pool significant amounts of blood in the extremities (Ebert and Stead, 1940). The resultant diminution of blood contained within the head and trunk is manifest by a fall in venous pressure (Warren and Stead, 1943). In addition, decreases in pressure have been observed in the chambers of the right heart and throughout the pulmonary circulation in both man (Doyle *et al.*, 1951) and animal (Henry *et al.*, 1956). The pressure gradients, however, remain relatively unchanged. Although observations on cardiac output have yielded somewhat varied results (McMichael and Sharpey-Schafer, 1944; Warren *et al.*, 1945; Fitzhugh *et al.*, 1953), it would appear most likely that there is a small decline in cardiac output. The striking change in apex impulse noted in our tracings would indicate an altered rate of ventricular filling. It has already been noted that the application of tourniquets to the extemities often results in the eradication of the physiological third heart sound (Sloan and Wishart, 1953). It is not surprising, therefore, that blood pooling has a similar effect on gallop sounds.

The exact mechanism producing the gallop sound is not understood. It has been suggested that it arises from vibrations in the pericardium, the wall of the ventricle, or from the valve leaflets themselves. A recent critical evaluation by Dock and his colleagues (1955) has led them to the conclusion that the valvular theory has more evidence in its support. On the other hand, there have been recent observations with intracardiac pressure tracings, which are interpreted as being more compatible with the wall thesis (Kuno *et al.*, 1957). The observations recorded here are not specifically in support of any one theory. They provide further evidence that the sound is indeed causally related to the influx of blood into the ventricular cavity. In theory, the disappearance of the gallop may be due to changes in the volume elasticity characteristics of the ventricle resulting from either a fall in intracavitary pressure, slowed ventricular filling, or perhaps diminished residual blood in the ventricle.

It is of interest to note the changes in the gallop sound that occur on tourniquet release. With the first appearance of the gallop it is of low amplitude. In the ensuing beats, as ventricular flow increases, the intensity is augmented and in some cases the sound is seen to migrate closer to the second heart sound. Such alterations in amplitude and timing with changes in ventricular inflow are reminiscent of changes observed by Mounsey (1955) in the early diastolic sound of constrictive pericarditis following successful operative therapy. Available evidence indicates that this latter sound represents an altered ventricular gallop. These observations are consistent with the thesis that factors related to pressure volume characteristics of the heart are important not only in determining the presence of a gallop sound, but its timing and sound characteristics.

In the course of the observations reported here, it became apparent that a practical usefulness was evolving. In certain patients there is a difficulty on clinical grounds in differentiation between a ventricular gallop and other sounds such as a split second sound or an opening snap of mitral stenosis. It has been our experience that tourniquet application which alters the ventricular gallop sound does not effect the opening snap or the splitting of the second sound (Warren *et al.*, 1957). The atrial (presystolic) gallop sound is also altered by the pooling of blood, but fortunately can usually be distinguished by simple auscultation.

Summary and Conclusions

The peripheral pooling of blood by venous occlusive tourniquets, with resultant alterations in pressure flow relationships within the heart, causes a diminution or disappearance of the ventricular gallop sound in most instances. This procedure may be useful in differentiating a ventricular gallop from an opening snap or a split second sound.

References

Dock, W., Grandell, F., and Taubman, F. (1955). *Amer. Heart J.*, **50**, 449.
Doyle, J. T., Wilson, J. S., Estes, E. H., and Warren, J. V. (1951). *J. clin. Invest.*, **30**, 345.
Ebert, R. V., and Stead, E. A. (1940). *J. clin. Invest.*, **19**, 561.
Fitzhugh, F. W., McWhorter, R. L., Estes, E. H., Warren, J. V., and Merrill, A. J. (1953). *J. clin. Invest.*, **32**, 1163.
Kuo, P. T., Schnabel, T. G., Jr., Blakemore, W. S., and Whereat, A. F. (1957). *J. clin. Invest.*, **36** 1035.
Henry, J. R., Gauer, O. H., and Sieker, H. O. (1956). *Circulation Research*, **4**, 91.
Leonard, J. J., Weissler, A. M., and Warren, J. V. (1957). *Circulation* (to be published).
McKusick, V. A. (1952). *Bull. Johns Hopkins Hosp.*, **90**, 27.
McMichael, J., and Sharpey-Shafer, E. P. (1944). *Brit. Heart J.*, **6**, 33.
Mounsey, P. (1955). *Brit. Heart J.*, **17**, 143.
Sloan, A. W., and Wishart, M. (1953). *Brit. Heart J.*, **15**, 25.
Warren, J. V., Brannon, E. S., Stead, E. A., and Merrill, A. J. (1945). *J. clin. Invest.*, **24**, 337.
——, Leonard, J. J., and Weissley, A. M. (1957). *Ann. intern. Med.* (to be published).
——, and Stead, E. A. (1943). *Amer. J. med. Sci.*, **205**, 501.
Wolferth, C. C., and Margolies, A. (1933). *Amer. Heart J.*, **8**, 441.

THE AORTIC LESION OF ANKYLOSING SPONDYLITIS

BY

B. M. ANSELL, E. G. L. BYWATERS, AND I. DONIACH

From the Postgraduate Medical School of London and Canadian Red Cross Memorial Hospital, Taplow

Received January 20, 1958

The occurrence of heart disease in rheumatoid arthritis and ankylosing spondylitis has been known for a considerable time, but its exact incidence and status has been the subject of much controversy, further confused by the North American inclusion of both diseases under one heading. In a survey of the subject in 1950, Bywaters distinguished three combinations: patients with rheumatoid arthritis and specific (rheumatoid) valve lesions; patients with both rheumatoid arthritis and, as a coincidence, rheumatic heart disease; and finally, patients with Jaccoud's syndrome (rheumatic heart disease and chronic post-rheumatic joint deformities). These three possibilities were also discussed by Thomas (1955) in relation to ankylosing spondylitis, and it was concluded that some of these patients were of the Jaccoud type. In his series of 12 cases with spondylitis and valvular disease, only two showed lone aortic disease, both with a previous history of rheumatic fever and thought to be rheumatic in origin; the remaining 10 presented mitral lesions predominantly. Only four cases of ankylosing spondylitis with necropsy were tabulated by Bywaters in 1950; one of them had mitral fibrosis without stenosis or regurgitation, and another calcified aortic valves. A larger series of cases has since been studied clinically (Wilkinson and Bywaters, 1958) and two patients have been found up to the present time presenting the aortic lesion described in "rheumatoid arthritis" (ankylosing spondylitis) by Bauer *et al.*, 1951. As these appear to be the first described in this country, a detailed account, including necropsy data on one, is thought to be of interest.

Case Reports

Case 1. A man, when aged 22 in 1944, developed pain and swelling of both feet. A diagnosis of rheumatoid arthritis was made and he was discharged from the Army, walking with the aid of sticks. His ankles and feet improved, but this was followed by pain and stiffness in the knees. At the end of a year he was symptom free and working full time as a lorry driver.

In 1947 he developed a right iritis. About 1949 he first noticed stiffness and aching in the lumbar and thoracic spine and when seen at Hammersmith Hospital was found to have a rigid spine with a chest expansion of 2 cm. At that time the E.S.R. was 74 mm./hr. Westergren, and the hæmoglobin 65 per cent. Narrowing of the sacroiliac joints and some marginal lipping of both hip joints were seen on X-ray films. He was treated by radiotherapy with good symptomatic effect.

He had further courses of radiotherapy in 1950 and twice in 1952. In 1951 the right iritis recurred, and despite local therapy he was left with severely impaired vision. At this time the spine was completely fixed. Despite an E.S.R. between 75 and 125 mm./hr. and mild anæmia, he was well enough to continue work as a lorry driver until early in 1954, when iritis appeared in the left eye; it was again treated locally, and caused further deterioration in vision. He had developed increasing flexion deformity of the right hip, and in October 1954, on entry into Hammersmith Hospital, in addition to the completely rigid spine he showed an attitude of general flexion, with limitation of both shoulder and hip joints and both knees. The chest expansion was now half an inch. The cardiovascular system was normal clinically, apart from a soft systolic murmur at the apex; blood pressure 135/70. There was slight œdema of the dorsum of both feet. There was bilateral and extensive old iritis but no evidence of active inflammation. Investigations revealed

E.S.R. (Westergren) 97 mm./hr., D.A.T. 1 : 4 (negative), mild hypochromic anæmia, and marrow compatible with iron deficiency anæmia; occult blood was positive on two occasions, but a barium meal was normal as was a fractional test meal. Rectal examination was negative. He was treated by oral iron with moderate response.

He became increasingly disabled because of severe hip involvement, and was admitted to Manor House Hospital in November 1955, where he remained until the beginning of October 1956, being treated with radiotherapy and prednisolone. At this time the heart was reported as normal. By the time he was discharged, now off hormone, he was able to walk without assistance, but rapidly relapsed so that by the time of re-admission here in November 1956 he was unable to do anything for himself, and was in severe pain. The lumbar and thoracic spine was rigid and flexed and there was slight movement in the cervical region only. Both shoulders were painful and limited and the hips fixed at about 90° flexion deformity. X-ray showed gross changes in spine, sacroiliac joints, and hips, typical of ankylosing spondylitis.

By now the pulse was of water hammer character and the blood pressure was 140/70. The apex beat was displaced to the left and of left ventricular type and there was a triple rhythm with an ejection murmur at the apex; also a loud aortic diastolic murmur (Fig. 1). Investigations: E.S.R. 85 mm./hr., D.A.T. 1 : 1; hæmoglobin 65 per cent; iron deficiency anæmia; barium meal negative; Wassermann and Kahn, treponema pallida immobilization test and Price precipitation reaction (kindly done for us at the V.D. Reference Laboratory) were all negative, as all our own tests had been. A chest X-ray showed no abnormality. The cardiogram showed partial right bundle-branch block with P–R interval 0·24 seconds.

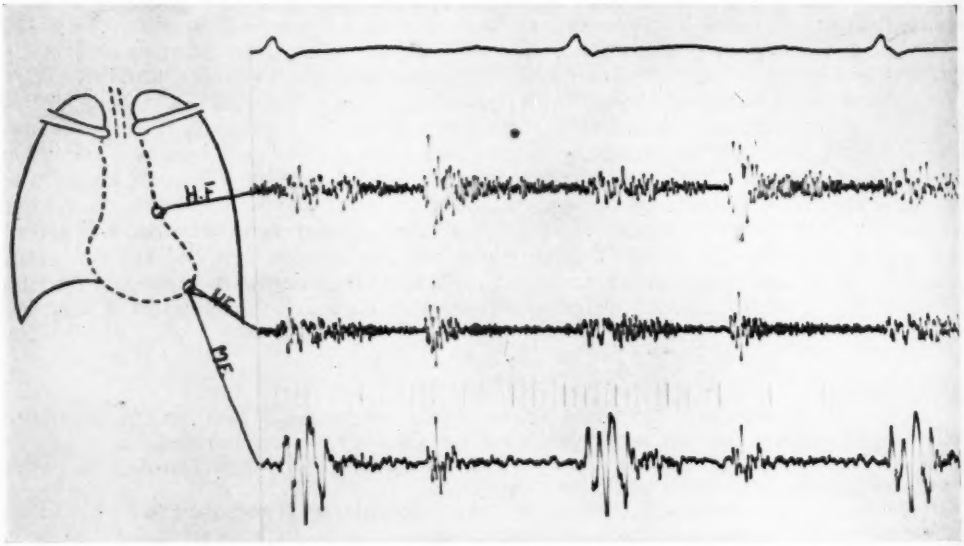


FIG. 1.—Case 1. Phonocardiogram, showing aortic diastolic murmur in a man aged 36 who had ankylosing spondylitis for 13 years.

The patient was given 15 mg. prednisolone daily, which was temporarily increased to 30 mg. a day together with dispirin and intensive physiotherapy. On this treatment he slowly improved so that it became possible for him to live at home and to get about well on elbow crutches. The eyes have improved only slightly and the cardiovascular system is clinically unchanged, but he has had several attacks of palpitation lasting about ten minutes, which are thought to have been paroxysmal tachycardia. There has been no evidence of cardiac failure.

Case 2. A man, aged 27, was first seen in 1949, complaining of pain in the right sacro-iliac region which had appeared every 10 to 14 days, persisting for two to three days over the last six months. He was febrile (temperature up to 103 °F.) and showed acute tenderness over the right sacro-iliac joint and right great

trochanter, but no other abnormal physical findings, the blood pressure being 130/84. Investigations showed an E.S.R. 122 mm./hr. (Westergren) and haziness in the right sacro-iliac joint on X-ray. The most likely diagnosis was thought to be tuberculous sacro-ileitis, but this could not be substantiated, the Mantoux being negative 1/100 and no abnormality seen on the chest X-ray. Over the next weeks he ran a persistently high E.S.R., and lost weight. Ten weeks after admission he developed pain and swelling of the right knee, and later of the right ankle and foot. At this time blood Wassermann and Kahn and gonococcal fixation tests were negative; aspiration of the synovial fluid showed low viscosity, 5·5 g. of protein per 100 ml.; white cell count 4400/cu. mm. with 98 per cent lymphocytes. Biopsy of the synovial membrane was compatible with, but not typical of, rheumatoid arthritis. At this time it was thought that the most likely diagnosis was an unusual form of rheumatoid arthritis, but the possibility of Reiter's syndrome had to be borne in mind. The patient continued to have pain and swelling of other peripheral joints (left knee, left ankle, and several toe joints), but steadily improved on salicylates, so that about six months from the time of admission he was completely well again and symptom free.

He then went to India, where from 1950 to 1953 he was quite well, working as a supervisor in the well-digging industry. In 1952 he developed a urethral sore, which was treated by a short course of penicillin injections. Shortly after his return in 1953 he was seen at Hammersmith Hospital when he appeared to be quite well and had had no further symptoms. No X-ray or blood examinations were made. In 1954 he developed left iritis. This was treated by local cortisone, and improved after two weeks only, to recur and require further treatment over a period of one year without any real recovery of sight in that eye.

The patient was seen again in November 1955. In the preceding four months he had become increasingly tired, and had severe exertional dyspnœa, with recurrent chest pain on exertion, and frequent nose bleeds. At this time he showed a jugular venous pressure of 3 cm. above the sternal angle, a collapsing pulse, blood pressure of 130/55, an apex beat displaced to the left, a triple rhythm, and a loud aortic diastolic murmur. The only other positive finding at this time was the old left iritis. There was no apparent peripheral joint abnormality and minimal limitation of back movement. He was advised admission to hospital but this he refused. However, he had to be admitted in February 1956 because the angina had become very much worse. There was no change in the physical signs recorded in the out-patient notes.

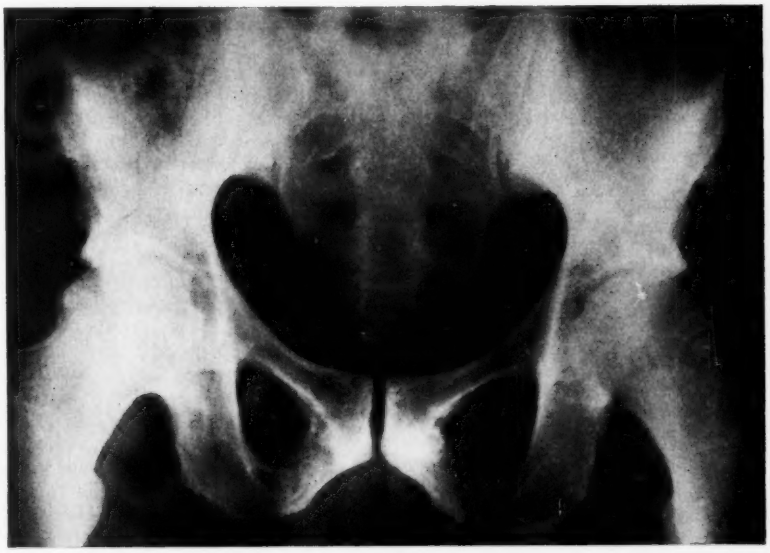


FIG. 2.—Case 2. Pelvis, showing obliterated sacro-iliac joint on one side with early erosions and subarticular sclerosis on the other. Note also hypertrophic bony outgrowths on ileum and ischiopubic rami.

The chest expansion was now 2 cm., having been 11 cm. in 1949. Investigations: E.S.R. 60 mm./hr. Westergren; total protein 7·8 g. albumin 3·4 g. globulin 4·4 g. each per 100 ml.; colloidal gold negative; zinc sulphate 5; D.A.T. 1 : 4; Wassermann and Kahn, Price precipitation and *Treponema* immobilization tests all negative. X-ray of the chest showed rounding of the left ventricular border with prominence of the left aortic knuckle. The joint X-rays showed complete obliteration of the right sacro-iliac joint, some bony sub-articular sclerosis in the region of the left, complete bridging between the second and third lumbar vertebra and early bridging elsewhere in the lumbar spine. The ischial and pubic rami showed characteristic bony excrescences (Fig. 2 and 3). There was an erosion of the terminal joint of the right big toe. In the electrocardiogram the P–R interval was 0·22 to 0·26 seconds with some depression of the S–T interval and marked changes of the T wave. This was thought to indicate a large left ventricle with probably some ischæmic changes or digitalis effect. He was treated with digitalis and bed rest and trinitrini with good effect.

FIG. 3.—Case 2. X-ray of spine (Feb. 1956), showing bridging L.2, 3 and early bridging T.12, L.1, L.2. Some sclerosis of apophyseal joints.

He was re-admitted twice more in 1956 for heart failure, with nocturnal and exertional dyspnœa and angina. The blood pressure rose gradually to 230/70; the liver became palpable and crepitations were heard at the bases. The heart became greatly enlarged. Treatment was continued with digitalis and neomercazole, until the recurrence of iritis in 1957, not responding to local hormone, necessitated the addition of prednisolone. This had to be discontinued after two weeks because of his psychotic behaviour. The jugular venous pressure rose, and peripheral œdema appeared, unresponsive to treatment; he died in April 1957 after the development of what was thought to be pulmonary infarction.

Post-mortem examination (Dr. Doniach) showed evidence of long-standing congestive heart failure with terminal pulmonary infarction. No other visceral changes except those in the heart were seen.

The heart weighed 515 g. and was dilated and hypertrophied, especially the left ventricle. The mitral valve showed congenital duplication of the posterior cusp but no other abnormality. The aortic cusps were thickened and the free margins rolled. The commissures were thickened, leading to regurgitation but not inter-adherent (Fig. 4). The other valves were healthy and the coronary arteries showed no atheroma although there was slight hyaline thickening of the first few proximal centimetres. The aorta showed patchy hyaline thickening (Fig. 5), down to below the renal arteries, especially round the orifices of branches, longitudinal wrinkling, and a few spider scars, closely resembling the changes of syphilis (although in the latter disease these changes seldom spread below the diaphragm).

Microscopically, infarction of the lungs was confirmed and there was congestive centrilobular necrosis in the liver. The eye showed chronic inflammatory iritis and cyclitis. The prostate showed no abnormality apart from some thrombus in the periprostatic veins. Examination of the knee, finger joints, sacro-iliac

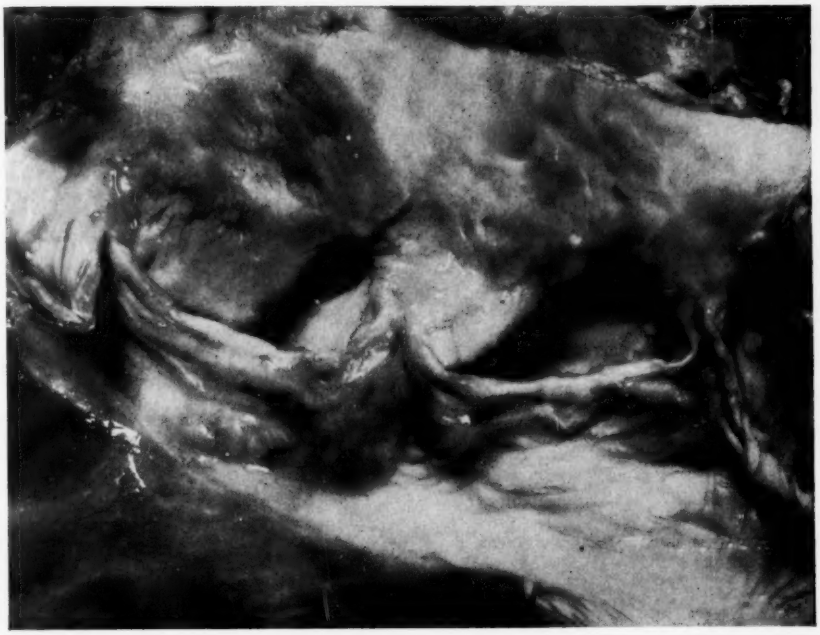


FIG. 4.—Aortic valve, showing thickening of the cusps, rolled free margins, thickening and separation of the commissures. The intima of the sinuses of Valsalva and ascending aorta is irregularly thickened and wrinkled. Case 2.

and apophyseal joints showed no present active inflammatory disease, although in the knee there was evidence of previous disease. The sacro-iliac joint and apophyseal joints also showed scarring with loss of cartilage and replacement by fibrotic connective tissue which also penetrated the sub-chondral bone in places. This tissue was quite distinct from the normal fibrous tissue bridging the upper part of the joint between the two bones.

The heart showed no Aschoff nodes or evidence of previous inflammatory disease in the neighbourhood of the mitral valve. The aortic valve (Fig. 6) showed collagenous thickening of the cusps from the free margin to the base. There were abnormal vessels in the cusp itself and in the epicardium surrounding the root of the aorta. The latter vessels showed gross thickening of the intima by the new formation of longitudinal muscle and elastic tissue internal to the internal elastic lamina, resulting in a very small lumen (Fig. 7 and 8). The aorta showed hyaline thickening of the intima and collagenous thickening of the adventitia with some cuffing of the vasa vasorum by lymphocytes. Some also showed intimal endarteritis. The media showed severe and widespread damage by both diffuse and focal collagenous replacement of muscle and elastic tissue usually surrounding small vessels (Fig. 9 and 10); in places, nuclei were absent. This change extended down to the mid-abdominal aorta (see Fig. 5.)

DISCUSSION

It is clear that both these patients developed the lesion that was described briefly by Bauer and his colleagues in 1951, and more fully by Clark *et al.* (1957). As Bauer claims, on more general grounds, this is not syphilis, since the *Treponema* immobilization test was negative in both instances (Zellmann, 1954). Bennett (1951) in discussion of Bauer's 1951 abstract cites a case of juvenile rheumatoid arthritis, commencing at the age of 3 and showing at the age of 8 at necropsy severe

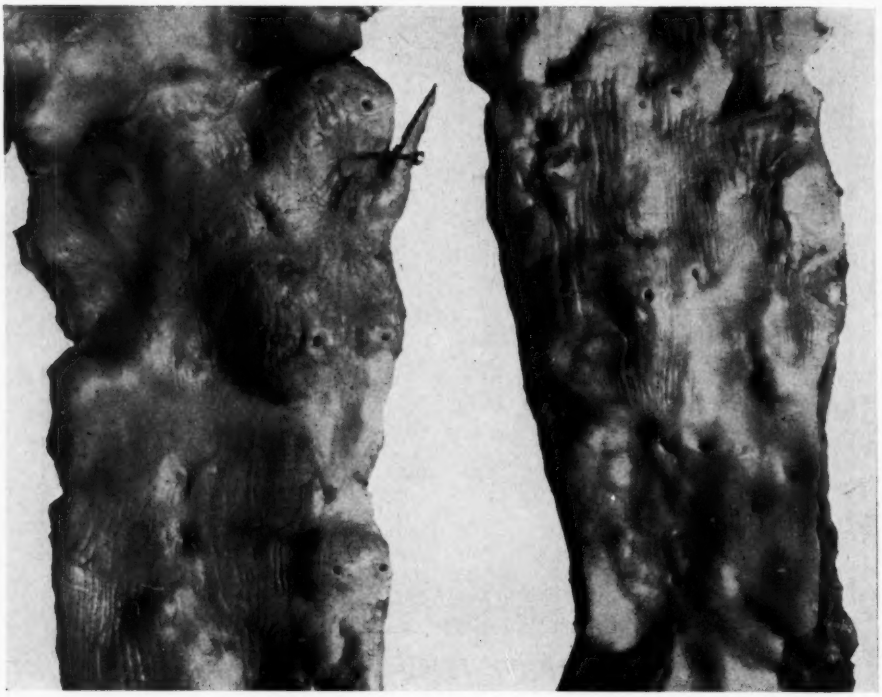


FIG. 5.—Thoracic aorta on the left, abdominal on the right, showing longitudinal wrinkling, scattered intimal plaques and occasional irregular intimal scars. These changes stop sharply a few cm. above the bifurcation. Case 2.

aortitis with aneurysm formation; the cusps were thickened and the proximal 3 cm. of aorta showed lesions "difficult if not impossible to distinguish from an actual syphilitic aortitis." In this, as in Bauer's cases and ours, the serological reactions were negative. We have also seen the development in juvenile rheumatoid arthritis (Still's disease) of basal diastolic murmurs and aortic regurgitation. At this age, sacro-iliac disease is difficult to diagnose radiologically or by other means. Three of the six cases described by Schilder *et al.* (1956) had symptoms in childhood at 3, 11, and 12 years of age, before developing spondylitis as young men and aortic lesions some years later.

It is of some interest that this complication developed in the two present cases at 7 and 12 years from the apparent onset. This compares with a duration of from 9 to 29 years in the Washington series. Both our patients showed a prolonged P–R interval and this has been present in five out of six of the Washington series and in six of the Boston series.

The incidence of this complication seems to be low. Thus, in a study of 530 patients at a spondylitis clinic, Sharp (1957) mentions patients with rheumatic heart disease and patients with Jaccoud's syndrome affecting the spine, but does not mention this aortic lesion. We ourselves in a follow-up and survey of 222 patients with ankylosing spondylitis (Wilkinson and Bywaters, in press) found only these two patients with lone aortitis, and two with rheumatic heart disease (mitral involvement) on clinical examination. This was with a mean follow-up period of 4·6 years and a mean duration of disease of about 12 years for the group as a whole. However, had we done the survey two years earlier we should have picked up neither of these two cases. This incidence is comparable to the figure given by Bernstein and Broch (1949): in 292 cases they found three with

FIG. 6.—Section of aortic valve, showing gross collagenous thickening of the cusp and ring. H. & E. × 8.

FIG. 7.—Epicardium over root of aorta. The vasa vasorum of the adventitia of the root of the aorta show striking intimal thickening. H. & E. × 57.

aortic regurgitation alone. Three more also had aortic stenosis and four had mitral stenosis (two with aortic regurgitation). There seems to be no reason why the large anterior leaf of the mitral valve should not be involved in contiguity as it sometimes is in syphilis, and indeed MacMahon *et al.* (1955) have described such a case. It should not however give rise to mitral stenosis, nor to much in the way of regurgitation.

The significance of this lesion is uncertain: it does not seem likely that patients with ankylosing spondylitis fail to develop a positive Wassermann and Kahn or *Treponema pallida* immobilization after infection with *T. pallida*, since when syphilis was more common, many such patients gave positive reactions. Thus Fletcher (1947) found positive tests in four of seventy patients. We do not think that our patients had Reiter's disease. Moreover, there is no relation to post-irradiation fibrosis, as our second case had no radiotherapy. Aortic scarring and vessel changes have been described in rheumatic heart disease (Shaw, 1929), but there was neither clinical nor pathological evidence for this. The lesion appears to be quite different from the aortic or mitral valve deformities associated with rheumatoid granulomata.

We must, therefore, agree with Bauer and his colleagues that this is a specific lesion and related in some way to the connective tissue changes that affect the central and peripheral joints in ankylosing spondylitis. It is well known that the aorta is rich in chondroitin sulphate, elastin, and collagen fibres, as are joint tissues, but we are not yet able to point to the component or components involved nor to the manner of its involvement. By analogy with the histological change of syphilitic aortitis, the localization of lesions may be related to the vascular supply.

FIG. 8.—Section of artery from adventitia of root of aorta, showing irregular musculo-elastic fibre formation within the intima. Weigert's elastic and Van Gieson × 185.

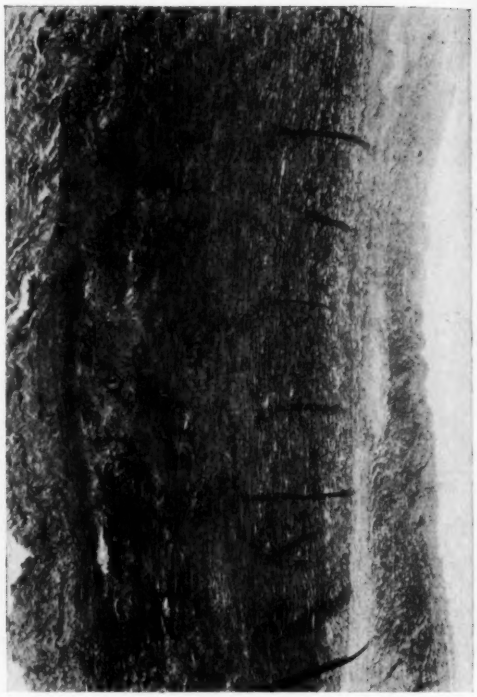


FIG. 9.—Aorta of which the adventitia (to left) and intima (to right) of the aorta are thickened; the elastic fibres of the media are interrupted by fibrous scar tissue in an irregularly shaped focus near the adventitia. Verhoeff's elastic × 57.

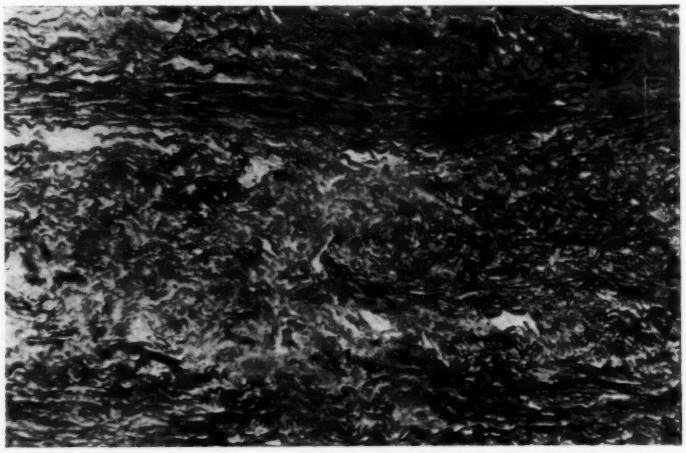


FIG. 10.—High power of Fig. 9, showing medial scar, due to focal interruption of the elastica by collagen. Verhoeff's elastic × 95.

Summary

Two patients with lone aortic disease, a prolonged P–R interval, and ankylosing spondylitis are described. One had congestive failure, from which he died, and histological study showed fibrotic lesions in the aortic valve cusps and in the aorta, similar to those described by Bauer and his colleagues. In both, the Wassermann, Kahn, *Treponema* immobilization and Price precipitation tests were negative. These two were the only cases found in a survey of 222 patients followed up for a mean period of 4·6 years.

We are grateful to Dr. Cope and other colleagues at the Postgraduate Medical School for some of the data on these patients, and to the Venereal Disease Reference Laboratory, Director, Dr. I. N. Orpwood-Price, for the specific tests.

References

Bauer, W., Clark, W. S., and Kulka, J. P. (1951). *Ann. rheum. Dis.*, **10**, 470.
Bennett, G. A. (1951). In discussion on Bauer, W., Clark, W. S., and Kulka, J. P. (1951).
Bernstein, L., and Broch, O. J. (1949). *Acta. med. Scand.*, **135**, 185.
Bywaters, E. G. L. (1950). *Brit. Heart J.*, **12**, 101.
Clark, W., Kulka, J. P., and Bauer, W. (1957). *Amer. J. Med.*, **22**, 560.
Fletcher, E. (1947). *Medical Disorders of the Locomotive System.* Edinburgh.
MacMahon, H. E., Magendantz, H., Brugsch, H. G., and Patterson, J. F. (1955). *Bull. Tufts New Engl. Med. Center*, **1**, 50.
Schilder, D. G., Harvey, W. P., and Hufnagel, C. A. (1956). *New Engl. J. Med.*, **255**, 11.
Sharp, J. (1957). *Brit. med. J.*, **1**, 975.
Shaw, A. F. B. (1929). *Arch. Dis. Child.*, **4**, 155.
Thomas, A. E. (1955). *Ann. rheum. Dis.*, **14**, 259.
Wilkinson, M., and Bywaters, E. G. L. (1958). In press.
Zellmann, H. E. (1954). *Amer. J. Syph.*, **38**, 506.

THE CEREBRAL BLOOD FLOW IN MITRAL STENOSIS AND ITS RESPONSE TO CARBON DIOXIDE

BY

H. A. DEWAR AND L. A. G. DAVIDSON

From the Department of Medicine, Royal Victoria Infirmary, Newcastle-upon-Tyne

Received March 11, 1958

Ever since Kety and Schmidt (1948) showed that the cerebral blood flow (C.B.F.) of normal subjects would increase when carbon dioxide was inhaled, such inhalation has had obvious possibilities in the treatment of cerebral embolism. As it has not been known whether this increase would still occur when mitral stenosis, the commonest cause of cerebral embolism, was present, it was decided to measure the C.B.F. at rest and again during inhalation of 5 per cent carbon dioxide in 12 patients with this disease (Series 1). Since these patients were also being studied as to their suitability for surgical treatment the opportunity was taken to compare the C.B.F. with the clinical status of the patients and with the hæmodynamic findings obtained by cardiac catheterization both at rest and during exercise. This report includes in addition estimations of the C.B.F. at rest of 13 other subjects who suffered from mitral stenosis and were having cardiac catheterization done (Series 2) and of 6 student volunteers who acted as controls (Series 3). The combined series show how the resting C.B.F. of patients with mitral stenosis differs from the normal.

Subjects, Methods, and Procedure

Details of the 12 subjects of Series 1 are given in Table I. None were in congestive heart failure or suffering from active rheumatism. The 13 subjects whose C.B.F. are given who did not inhale CO_2 include six from a series previously reported (Dewar *et al.*, 1953). Six of the other seven patients were from a series not previously published and had been given a dosage of nitroglycerine which proved to be without influence on the C.B.F.; these latter six may be regarded as controls for the reproducibility of the method. None of the subjects in Series 2 or Series 3 were given morphine at any stage of their C.B.F. estimations.

Cerebral Blood Flow was estimated by the nitrous oxide method of Kety and Schmidt (1948), and their standard gas mixtures were used. For Series 2 Scheinberg and Stead's (1949) modification of this technique was used but with corrections for the dead space of the catheter and connecting tubing so as to render the result comparable (Stroud *et al.*, 1954). In all three series the cerebral venous blood samples were collected through a cardiac catheter whose end had been placed in the superior jugular bulb according to the technique described by Dewar *et al.* (1953). Nitrous oxide content of blood was estimated in a Van Slyke manometric apparatus for Series 2 and 3, but for Series 1 where the number of estimations was larger the method of Lawther and Bates (1953), using an infra-red analyser, was substituted; its accuracy was first checked against the Van Slyke apparatus. All samples were analysed in duplicate.

Oxygen Consumption was measured by collection of expired air into Douglas bags. Duplicate air samples were analysed in a Haldane gas apparatus and the oxygen uptake calculated by standard methods.

Oxygen Content of Blood. The hæmoglobin percentage saturation was measured by the method of Molyneux and Pask (1955), slightly modified. The oxygen content and capacity were deduced from the percentage saturation and the hæmoglobin concentration, measured photometrically.

Pressure Recording. Intra-cardiac pressures were recorded on an Elmquist strain gauge manometer, zero being fixed at the subject's sternal angle. Brachial artery pressures were taken with a mercury sphygmomanometer, mean pressures being taken as the diastolic plus a third of the pulse pressure.

Proceedure. No preliminary sedatives were given but quinidine, 0·2 to 0·3 g., was given to those having cardiac catheterization in order to prevent arrhythmias. To the subjects of Series 1 whose investigation took an exceptionally long time a light breakfast of tea and toast was permitted. In the subjects of Series 2 cardiac catheterization was followed after a rest period of at least 45 minutes by an estimation of C.B.F. (13 patients) and after a further half hour's rest by a duplicate estimation (6 patients).

In the subjects of Series 1 to whom exercise was to be given the catheter was continually flushed with a small quantity of 0·1 per cent procaine solution as an additional precaution against

TABLE 1

CARDIOVASCULAR HÆMODYNAMICS OF SERIES 1

Subject	Cardiac rhythm	Digitalis	Functional grading		Pressures (mm. Hg)		Oxygen saturation %		Cardiac index (l/min/ M²)	Calculated mitral valve area (cm.²)	Operation findings
					Pulmonary artery (mean)	Pulmonary capillary (mean)	Brachial artery	Pulmonary artery			
1. E. B. (M)	S.R.	No	I	Rest	20	11	92	61	2·8	1·6	
				Ex.	30	—	93	57	7·8		
2. M. W. (F)	S.R.	No	IV	Rest	17	12	96	73	3·4	1·9	
				Ex.	38	—	97	62	4·1		
3. M. H. (F)	A.F.	Yes	III(a)	Rest	39	27	98	73	2·7	0·9	M.S. +++
				Ex.	48	—	92	55	3·9		
4. N. R. (M)	S.R.	No	IV	Rest	25	21	93	69	3·6	1·4	
				Ex.	30	—	84	c. 33	?3·0		
5. L. F. (F)	S.R.	No	III(a)	Rest	10	Not obt.	97	73	3·0	—	
				Ex.	12	—	97	c. 58	?3·0		
6. R. M. (M)	S.R.	No	II	Rest	8	6	96	76	3·6	>2·5	
				Ex.	17	—	95	48	3·5		
7. J. Mor. (M)	S.R.	Yes	III(b)	Rest	28	18	91	59	2·9	2·2	
				Ex.	52	—	88	38	5		
8. G. W. (M)	A.F.	Yes	II	Rest	20	14	92	67	2·8	1·6	M.S. ++
				Ex.	30	—	91	c. 32	?3·6		
9. A. W. (M)	S.R.	Yes	III(a)	Rest	42	22	88	64	2·5	0·9	M.S. +++
				Ex.	72	—	88	c. 38	?2·7		
10. J. F. (M)	S.R.	No	III(b)	Rest	32	20	93	68	2·5	1·0	M.S. +++ M.I. + A·S. +
				Ex.	54	—	90	47	6·8		
11. J. Mos. (M)	A.F.	Yes	III(b)	Rest	30	Not obt.	86	52	1·9	—	M.S. +++ M.I. +
				Ex.	61	—	76	24	2·3		
12. T. W. (F)	A.F.	Yes	III(a)	Rest	18	15	92	76	4·1	1·7	M.S. ++
				Ex.	28	—	93	53	4·1		

S.R. = Sinus rhythm
A.F. = Auricular fibrillation
M.S. = Mitral stenosis
M.I. = Mitral regurgitation
A.S. = Aortic stenosis

arrhythmias, but this was exchanged for normal saline as soon as the cardiac catheterization was over so that its action would not interfere with the subsequent C.B.F. estimation, though Scheinberg *et al.* (1952) have shown that procaine has an insignificant effect upon C.B.F. When during the catheterization repeated pressure records showed that a steady state of pulse and pressure was present, the resting cardiac output was measured by the direct Fick principle. The patients then exercised in the recumbent position on an ergometer (Bronfin, Dressler, and Ravin, 1950) to the level which previous trials had shown to be the most they could sustain steadily for five minutes. During the last three minutes of this exercise multiple blood samples were taken from the pulmonary and brachial arteries whilst the expired air was collected in a Douglas bag so that the cardiac output could again be estimated. Morphine, 0·01 g., was then given intravenously to allay restlessness and after a rest period of at least 45 minutes the C.B.F. was estimated. Thirty minutes later a second estimation of C.B.F. was made during the inhalation of 5 per cent carbon dioxide using the same gas mixture (CO_2 5 per cent, N_2O 15 per cent, N_2 59 per cent, O_2 21 per cent) as was used by Kety (1948) in his studies on the effect of carbon dioxide on cerebral blood flow in normal subjects, but without his preliminary saturating inhalation of carbon dioxide in air. By an unfortunate oversight systemic blood pressure readings during these C.B.F. studies were taken on only 6 of the subjects in this series.

TABLE II

CEREBRAL HÆMODYNAMICS IN MITRAL STENOSIS AND RESPONSE TO INHALATION OF CARBON DIOXIDE (Series 1)

Subject	Sex and age	Resting					Inhaling 5% CO_2					Percentage increase of C.B.F.	Actual increase of C.B.F.
		C.B.F.	A-V O_2	C.M.R.O_2	M.A.B.P.	C.V.R.	C.B.F.	A-V O_2	C.M.R.O_2	M.A.B.P.	C.V.R.		
1. E. B.	M 17	48	—	—	—	—	63	—	—	—	—	+31	+15
2. M. W.	F 32	43	5·8	2·5	76	1·8	52	5·2	2·7	81	1·6	+21	+9
3. M. H.	F 35	34	8·2	2·8	70	2·0	45	7·0	3·2	83	1·8	+32	+11
4. N. R.	M 35	38	—	—	—	—	52	—	—	—	—	+37	+14
5. L. F.	F 39	42	5·7	2·4	85	2·0	52	4·2	2·2	80	1·5	+24	+10
6. R. M.	M 39	24	11·3	2·7	—	—	49	6·0	3·0	—	—	+104	+25
7. J. Mor.	M 44	34	—	—	—	—	43	—	—	—	—	+26	+9
8. G. W.	M 42	29	10·4	3·0	80	2·8	36	8·0	2·9	95	2·6	+24	+7
9. A. W.	M 45	42	6·2	2·6	73	1·8	40	6·6	2·6	84	2·1	− 5	−2
10. J. F.	M 46	43	5·4	2·3	82	1·9	44	5·8	2·6	96	2·2	+2	+1
11. J. Mos.	M 49	34	8·3	2·8	—	—	45	5·2	2·3	—	—	+32	+11
12. T. W.	F 52	23	—	—	—	—	34	—	—	—	—	+48	+11
Mean Values	40	36	7·7	2·6	78	2·1	46	6·0	2·7	87	2·0	+31	+10

C.B.F. = Mean cerebral blood flow (ml./100 gm. brain/min.).
A-V O_2 = Mean arterial-cerebral venous oxygen difference (ml. O_2/100 ml. blood) over ten-minute period.
C.M.R. O_2 = Mean cerebral oxygen consumption (ml. O_2/100 gm. brain/min.).
M.A.B.P. = Mean arterial blood pressure (mm. mercury) over ten-minute period.
C.V.R. = Mean cerebral vascular resistance (mm. mercury/one ml. blood/100 gm. brain/min.) over ten-minute period.

RESULTS

The results are given in Tables I–IV, and full details of the subjects exercised in Table I.

The C.B.F. was measured twice in 6 patients of Series 2, the differences affording useful evidence of the repeatability of the method. The standard deviation of these repeat measurements is 4·3 ml., and this with 6 degrees of freedom means that at the usual 95 per cent confidence level a single observation will lie within $\pm$ 10 ml. of the true value. From the data given by Kety and Schmidt in their original series (1948) the standard deviation of repeat estimations on the same side in the same case can be shown to be 4·6 ml.

TABLE III

CARDIAC STATUS AND CEREBRAL HÆMODYNAMICS IN MITRAL STENOSIS (Series 2)

Subject	Sex and age	Cardiac rhythm	Digitalis	Functional grading	Pulmonary artery mean pressure (mm. Hg)	Operation findings	C.B.F.		A-V O_2		CMR O_2		M.A.B.P.		C.R.V.	
							1	2	1	2	1	2	1	2	1	2
1. M. S.	F 29	S.R.	No	III(b)	64	M.S. ++	38	—	—	—	—	—	75	—	2·0	—
2. E. C.	F 38	A.F.	Yes	III(a)	29	M.S. ++	42	—	—	—	—	—	77	—	1·8	—
3. N. S.	F 22	S.R.	Yes	II	20+	M.S. ++ M.I. ++	58	—	—	—	—	—	81	—	1·4	—
4. M. G.	F 32	S.R.	No	III(a)	45+	—	48	—	—	—	—	—	91	—	1·9	—
5. E. G.	F 38	A.F.	Yes	IV	65+	M.S. ++	28	—	—	—	—	—	78	—	2·8	—
6. W. R.	M 39	S.R.	No	IV	66	M.S. +++	47	—	—	—	—	—	93	—	2·0	—
7. F. G.	M 49	A.F.	Yes	III(a)	25	M.S. +++ M.I. +	37	—	—	—	—	—	—	—	—	—
8. G. W.	M 38	A.F.	Yes	III(a)	29	M.S. +++	39	35	—	—	—	—	80	84	2·1	2·4
9. O. A.	F 25	S.R.	Yes	III(b)	29	M.S. ++	51	40	8·2	8·2	4·2	3·3	78	85	1·5	2·1
10. F. I.	F 29	S.R.	No	III(a)	—	M.S. +	63	57	8·3	8·7	5·2	5·0	91	95	1·5	1·7
11. H. B.	M 35	A.F.	Yes	III(b)	77	M.I. ++	27	33	8·2	8·1	2·2	2·7	96	95	3·6	2·9
12. J. C.	M 31	A.F.	Yes	III(a)	23	M.S. ++	30	27	6·0	6·8	1·8	1·8	90	92	3·0	3·4
13. F. S.	M 35	S.R.	No	III(a)	25	M.S. +++	29	28	11·3	11·3	3·2	3·1	91	84	3·2	3·0
Mean values	34	—	—	—	—	—	41	37	8·4	8·6	3·3	3·2	85	89	2·2	2·3

C.B.F. = Mean cerebral blood flow (ml./100 gm. brain/min.).
A-V O_2 = Mean arterial-cerebral venous oxygen difference (ml. O_2/100 ml. blood) over ten-minute period.
C.M.R. O_2 = Mean cerebral oxygen consumption (ml. O_2/100 gm. brain/min.).
M.A.B.P = Mean arterial blood pressure (mm. mercury) over ten-minute period.
C.V.R. = Mean cerebral vascular resistance (mm. mercury/ one ml. blood/100 gm. brain/min.) over ten-minute period.
S.R. = Sinus rhythm.
A.F. = Auricular fibrillation.
M.A. = Mitral stenosis
M.I. = Mitral incompetence.

TABLE IV

CEREBRAL HÆMODYNAMICS IN NORMAL SUBJECTS
(Series 3)

Subject	Sex	Age	C.B.F.	A-V O_2	C.M.R. O_2	M.A.B.P.	C.V.R.
J. Co.	M	21	50	7·8	4·0	83	1·9
J. Ca.	M	22	56	7·1	4·0	96	1·5
J. M.	M	22	44	7·4	3·3	87	2·0
M. R.	M	22	51	5·3	2·7	70	1·4
E.R.	M	23	65	4·9	3·2	102	1·6
J. S.	M	24	72	5·6	4·0	90	1·3
Mean		22	56±10	6·4±1·2	3·5±0·6	88±11	1·6±0·3

C.B.F. = Mean cerebral blood flow (ml./100 gm. brain/min.).
A-V O_2 = Mean arterial-cerebral venous oxygen difference (ml. O_2/100 ml. blood) over ten-minute period.
C.M.R. O_2 = Mean cerebral oxygen consumption (ml.O_2/100 gm. brain/min.).
M.A.B.P. = Mean arterial blood pressure (mm. mercury) over ten-minute period.
C.V.R. = Mean cerebral vascular resistance (mm. Hg/one ml. blood/100 g. brain/min.) over ten-minute period.

These results show that the resting C.B.F. in cases of mitral stenosis is low. The mean C.B.F. of Series 1 and 2 is 39 ml./min./100 g. of brain, S.D. $\pm$ 12, compared with the figure of 56 ml., S.D. $\pm$ 10, from the normal subjects of Series 3 and with Kety and Schmidt's normal figure of 54 $\pm$ 12. The difference is highly significant, $P < 0{\cdot}01$. In the patients whose hearts were in sinus rhythm the C.B.F. was higher, 43 ml./min./100 g. than in those whose auricles were fibrillating, 32 ml./min./100 g.

The low C.B.F. of these cases of mitral stenosis is associated with a much increased cerebral vascular resistance, 2·2 mm. Hg/ml. blood/min./100 g. brain tissue (Series 1 and 2) compared with the normal of 1·6 mm. (Series 3, and Kety and Schmidt, 1948), but an only slightly decreased blood pressure—85 mm. Hg. in Series 1 and 2 and 88 mm. Hg in Series 3.

If morphine is not given the oxygen consumption of the brain remains normal at 3·3 ml./min./100 g.

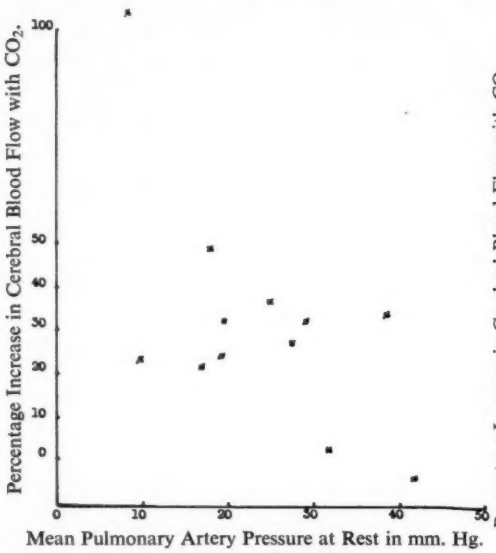


FIG. 1.—Graph showing relationship between resting pulmonary artery pressure and increase in C.B.F. induced by inhalation of CO_2.

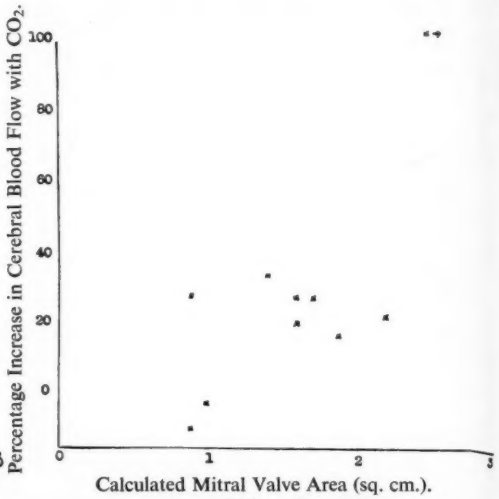


FIG. 2.—Relation between percentage increase in cerebral blood flow with CO_2 and calculated mitral valve area.

of brain tissue (Series 2) and this is made possible by an increased oxygen extraction by the tissues such as occurs in other parts of the body in mitral disease (Donald *et al.*, 1954), resulting in an increased arterio-jugular venous oxygen content difference of 8·5 ml. per 100 ml. compared with the normal of 6·4 ml. per 100.ml. If morphine is given as in Series 1 then the oxygen consumption falls, 2·6 ml./min./100 g. of brain tissue, as has been found in normal subjects by others (Moyer *et al.*, 1957), and the arteriovenous oxygen content difference correspondingly decreases, 7·7 ml. per 100 ml.

On inhalation of carbon dioxide the C.B.F. of the 12 cases of Series 1 increased by a mean extent of 31 per cent. The increase occurred in 10 out of the 12 subjects tested, a change that is statistically significant, $P < 0{\cdot}01$. Of the 6 subjects upon whom information was obtained the mean arterial blood pressure rose in 5 and the cerebral vascular resistance declined in 4.

Attempts to correlate the resting C.B.F. with any of the observed factors in the hæmodynamic studies, namely the functional grading, pulmonary artery pressure at rest and on exercise, pulmonary capillary pressure, arterial-mixed venous oxygen content difference, percentage saturation mixed venous blood, and cardiac index at rest and on exercise were completely unsuccessful.

A similar failure was encountered with the figure for C.B.F. during the inhalation of carbon dioxide. When, however, the resting pulmonary artery pressure was plotted against the percentage increase in C.B.F. induced by CO_2 inhalation a significant, $P<0{\cdot}05$, inverse relationship appeared (Fig. 1). When the mitral valve area of these same cases was calculated by the method of Gorlin and Gorlin (1951) and also plotted against the increase of C.B.F. induced by the inhalation, a rather more significant, $P<0{\cdot}02$, and this time direct, relationship was observed (Fig. 2).

Discussion

Technique. The average age of the 6 student volunteers who acted as normal controls was much less than those of the subjects suffering from mitral stenosis, but it has been shown that cerebral blood flow does not change significantly with age below 45 years (Heyman *et al.*, 1953) and the C.B.F. and other parameters in this normal series agree closely with those of other investigators (Kety and Schmidt, 1948; Shenkin and Novack, 1954).

The subjects of Series 1 whose investigations took an exceptionally long time to complete were not in a truly basal state during the study of their cardiovascular hæmodynamics and this may have affected the results even though only one of them (No. 12) had a resting cardiac index much above the normal.

The cardiac outputs during exercise were estimated as the mean of the last three minutes of a five-minute period since Donald *et al.* (1954) found by minute-to-minute studies of cardiac output during exercise in a similar group of rheumatic patients that 12 out of 16 attained a steady state of arterio-venous oxygen differences and of oxygen uptake within two minutes of the start. In the present series the proportion was very similar, 8 out of 12. A longer period of exercise would have been very poorly tolerated and two of the subjects could only complete 4 minutes; in Case 4 this was due to the development of pulmonary œdema. The derived cardiac outputs of them and of two other subjects who also did not attain a steady state are therefore distinguished by a question mark in Table I and the figures given for the oxygen saturation of their pulmonary artery blood are approximations only.

Results. The low figure for cerebral blood flow and the high arterio-jugular venous oxygen content difference in these cases of mitral stenosis is in keeping with the reduction of regional blood flow to other areas which Donald *et al.* (1954) have found in a similar series of cases. It is produced predominantly by an increase of cerebro-vascular resistance and is associated but not closely correlated with the reduction of cardiac output usually found in such patients (Ferrer *et al.*, 1952). It is of interest that the mean cerebral blood flow of seven cases of mitral stenosis in heart failure collected from previously reported cases (Scheinberg, 1950; Novack, 1953; Moyer *et al.*, 1952) is 40 ml./min./100 g. compared with the figure of 39 ml. reported here for patients not in failure, and this correlates well with the finding of Novack (1953) that in cases of cerebral arteriosclerosis the C.B.F. was not significantly different whether the subjects were in failure or not. Further investigation, in particular determination of *p*H and of pCO_2 values would be needed to show whether the increased cerebral vascular resistance in mitral stenosis is induced by the hyperventilation which is commonly found in this disease (Ferrer *et al.*, 1952); in the present group of cases (Series 1) the mean resting ventilation at 3·8 l./sq. metre/min. at standard pressure and body temperature was normal.

The 31 per cent mean increase of C.B.F. on inhalation of 5 per cent CO_2 was less than the 41 per cent increase observed by Novack *et al.* (1953) and much less than the 75 per cent increase noted by Kety and Schmidt (1948), but since Kety's preliminary saturating mixture of CO_2 in air was not given before the estimation of C.B.F. was begun this must be considered a minimum figure. It did not correlate closely with most of the cardiovascular parameters examined, but the pulmonary artery pressure at rest and the calculated mitral valve area did have a statistically significant relationship to it. In the case of the calculated mitral valve area (which is independent of the basal state of the subject and calculated from figures obtained at rest) the relationship was more significant, $P<0{\cdot}02$,

than in the case of the pulmonary artery pressure, but even so the form of this relationship was largely determined by three extreme figures, the remainder lying rather closely together, so that too much should not be made of it.

These results do suggest that inhalation of 5 per cent carbon dioxide in air could be a useful therapeutic measure in the treatment of cerebral embolism. Whether such treatment could be instituted promptly enough and without deleterious effect on the patient's cardiovascular system or general condition are, however, questions that still remain to be answered.

Summary

The cerebral blood flow was measured by the nitrous oxide technique in two series of 12 and 13 subjects suffering from mitral stenosis and was found to be significantly less than normal owing to an increase in the cerebral vascular resistance. The oxygen consumption of the brain was normal, however, unless morphine had been given when it was found to be depressed.

On inhalation of 5 per cent carbon dioxide in air by the 12 patients of one series, the cerebral blood flow increased by a mean of 31 per cent. The degree of this increase appeared to be related to the calculated mitral valve area and also, inversely, to the resting pulmonary artery pressure but not to the other hæmodynamic factors estimated at rest and on exertion.

It is suggested that inhalation of 5 per cent carbon dioxide merits further study as a means of treating cerebral embolism when it occurs in patients suffering from mitral stenosis.

This work was carried out during the tenure by one of us (L.A.G.D.) of a Luccock Fellowship of King's College in the University of Durham. Our thanks are due to Professor A. A. Harper and the Staff of the Department of Physiology for the construction of the ergometer and for loan of apparatus, to Dr. S. W. Davidson and Dr. C. K. Warrick for radiological facilities, to Dr. N. R. Rowell for technical assistance, to Mr. D. J. Newell for much help and advice on statistics, to the medical students who acted as volunteers for the normal C.B.F. estimations, and to Dr. S. G. Owen and Mr. A. R. Jenkins for permission to use some of their figures.

References

Bronfin, G. F., Dressler, S. H., and Ravin, A. (1950). *J. Lab. clin. Med.*, **35**, 317.
Dewar, H. A., Owen, S. G., and Jenkins, A. R. (1953). *Lancet*, **1**, 867.
Donald, K. W., Bishop, J. M., and Wade, O. L. (1954). *J. clin. Invest.*, **33**, 1146.
Ferrer, M. I., Harvey, R. M., Cathcart, R. T., Cournand, A., and Richards, D. W. (1952). *Circulation*, **6**, 688.
Gorlin, R., and Gorlin, M. E. (1951). *Amer. Heart J.*, **41**, 1.
Heyman, A., Patterson, J. L., Duke, T. W., and Battey, L. L. (1953). *New Eng. J. Med.*, **249**, 223.
Kety, S. S., and Schmidt, C. F. (1948). *J. clin. Invest.*, **27**, 476, 484.
Lawther, P. J., and Bates, D. V. (1953). *Clin. Sci.*, **12**, 91.
Molyneux, L., and Pask, E. A. (1955). *Brit. Heart J.*, **17**, 169.
Moyer, J. H., Miller, S. I., Tashnek, A. B., and Bowman, R. (1952). *J. clin. Invest.*, **31**, 267.
——, Pontius, R., Morris, G., and Hershberger, R. (1957). *Circulation*, **15**, 379.
Novack, P. (1953). *Circulation*, **7**, 725.
——, Shenkin, H. A., Bortin, L., Goluboff, B., and Soffe, A. M. (1953). *J. clin. Invest.*, **2**, 696.
Scheinberg, P., and Stead, E. A., jun. (1949). *J. clin. Invest.*, **28**, 1163.
—— (1950). *Amer. J. Med.*, **8**, 148.
——, Jayne, H. W., Blackburn, L. I., and Rich, M. (1952). *Arch. Neurol. Psychiat.*, 68, 815.
Shenkin, H. A., and Novack, P. (1954). *Arch. Neurol. Psychiat.*, **71**, 148.
Stroud, M. W., Lambertsen, C. J., Wendel, H., and Daly, M. de B. (1954). *Fed. Proc.*, **13**, 147.

THE EFFECT OF VALVOTOMY ON THE MURMURS OF PULMONARY AND AORTIC STENOSIS

BY

BERTRAND G. WELLS

From St. Bartholomew's Hospital

Received December 27, 1957

It is not generally accepted that the character of the systolic murmur of pulmonary or aortic stenosis gives an indication of the severity of the stenosis. This is probably because the intensity of the murmur has attracted more interest than the timing and character of the vibrations. Greene *et al.* (1949) state that a systolic thrill was present in half their cases of idiopathic dilatation of the pulmonary artery. Despite this finding there have been a number of authorities who have claimed that the loudness of the systolic murmur is proportional to the severity of the stenosis (Currens *et al.*, 1945; Dow *et al.*, 1950; Donzelot *et al.*, 1954; Mannheimer and Jonsson, 1954). Downing (1956) and Bailey *et al.* (1956) have found the murmur of aortic stenosis softer after aortic valvotomy.

The more widespread use of phonocardiography has enabled the duration of the systolic murmurs to be measured. Vogelpoel and Shrire (1955) have suggested that in cases of tetralogy of Fallot the duration of the murmur is inversely proportional to the severity of the stenosis. Mannheimer and Jonsson (1954) found that the peak intensity of the murmur of severe valvular pulmonary stenosis was later than that of moderate stenosis, but they did not comment on the duration of the murmurs.

There has been little interest in the frequency of the vibrations constituting the systolic murmurs of valvular and infundibular stenosis. The statements by Downing (1956) and Bailey *et al.* (1956) that the murmur of aortic stenosis is softer after valvotomy could be interpreted as an indication that the frequency is lower, but the term "softer" has probably been used to describe intensity rather than pitch. Mannheimer and Jonsson (1954) state that the murmur of pulmonary stenosis is of higher frequency than an innocent systolic murmur, but they have not related the frequency to the severity of the stenosis.

The relationship of the systolic murmur to the pulmonary and aortic components of the second heart sound has been the subject of considerable attention. Ordway *et al.* (1950) point out that in extreme pulmonary stenosis the pressure in the pulmonary artery may be lower than that in the right ventricle in both diastole and systole. It is therefore surprising that a continuous murmur is not audible in such cases. Reinhold and Nadas (1954) found that the murmur did extend into diastole in the most severe cases of pulmonary stenosis. Kjellberg *et al.* (1955) considered that stenosis of the infundibulum causes a longer silent interval between the end of the murmur and the pulmonary component of the second heart sound than is found in pulmonary valvular stenosis.

The present study was made to determine what changes are present in the systolic murmur after an operation to relieve valvular or infundibular stenosis. The changes were found to be definite. They showed that the severity of valvular stenosis could be assessed by studying the frequency of the vibrations and their timing in systole. The systolic murmur of infundibular stenosis changed after infundibular resection in a different manner from that of valvular stenosis after valvotomy. This throws light on the mechanism of prodution of these murmurs.

Material and Methods

Twenty patients undergoing surgical treatment of valvular or infundibular stenosis by Mr. O. S. Tubbs and Mr. I. M. Hill were studied. Three patients had an aortic valvotomy, combined in two cases with mitral valvotomy. Six patients had a pulmonary valvotomy for valvular pulmonary stenosis with a normal aortic root. Five patients had a pulmonary valvotomy for tetralogy of Fallot with valvular stenosis. Five patients had an infundibular resection for tetralogy of Fallot with infundibular stenosis. One patient had both a valvotomy and an infundibular resection for tetralogy of Fallot with valvular and infundibular stenosis. The age and sex of each patient are shown in Table I.

TABLE I

Analysis of Murmurs of Valvular and Infundibular Stenosis before and after Operation in 20 Patients

Diagnosis	Patient		Before relief of stenosis							After relief of stenosis						
	Case No.	Age and sex	Duration	Peak	Relation to A2	A2 to P2	Frequency	Total vibrations	Gradient	Duration	Peak	Relation to A2	A2 to P2	Frequency	Total vibrations	Gradient
Aortic stenosis	1	38 F	22	18	B	—	220	62	85	20	15	B	—	150	30	40
	2	45 F	25	17	B	—	210	53	100	17	15	B	—	190	32	35
	3	44 F	19	17	B	—	200	38	45	18	14	B	—	120	22	15
Pulmonary stenosis with normal aortic root	4	15 M	28	17	A	9	190	53	56	20	14	A	5	120	24	39
	5	16 F	29	19	A	15	220	64	100	22	15	O	8	170	37	20
	6	16 F	33	32	A	9	200	66	60	21	15	A	5	190	40	15
	7	13 F	25	20	A	8	210	53	18	20	10	A	4	160	32	4
	8	10 M	34	25	A	16	200	68	—	27	20	A	7	190	51	—
	9	36 F	34	18	A	10	200	68	—	32	16	A	9	170	54	—
Tetralogy of Fallot (*a*) Valvular	10	4 M	20	14	O	—	210	42	72	18	13	B	—	140	25	71
	11	12 F	28	25	A	12	230	64	132	27	20	O	7	180	50	133
	12	6 M	24	19	O	12	190	46	64	20	10	B	7	160	32	38
	13	5 M	21	15	B	—	240	50	57	11	8	B	—	200	22	30
	14	7 M	21	13	B	—	170	36	—	18	10	B	7	170	31	—
(*b*) Infundibular	15	14 F	24	25	O	—	210	50	57	23	12	O	12	150	35	43
	16	16 M	25	14	O	7	220	55	38	31	12	O	10	160	50	35
	17	9 M	26	16	O	—	230	60	51	26	15	O	10	160	42	45
	18	5 F	20	10	B	—	210	42	—	21	8	B	—	180	38	—
	19	9 M	23	15	A	7	280	64	—	29	15	A	10	200	58	—
(*c*) Valvular and infundibular	20	5 M	25	18	O	9	210	53	—	23	12	O	11	160	37	—

The duration of the murmur is measured in hundredths of a second. The peak is the interval in hundredths of a second between the onset of the maximal vibrations of the first heart sound and the point of maximal intensity of the murmur. Relation to A2 shows whether the murmur ends before (B), after (A), or at (O) the beginning of the aortic component of the second heart sound. A2 to P2 is the interval between the aortic and pulmonary components of the second heart sound. The frequency is in cycles a second. The total vibrations are the frequency times the duration. The gradient is measured in mm. Hg by direct puncture at the time of operation.

Logarithmic (high frequency) phonocardiograms were taken before and after operation. The post-operative tracings were obtained at least two weeks after operation. The tracings were taken on a Sanborn Stethocardiette using a technique previously described (Wells *et al.*, 1949). The patients were supine and stopped breathing at the end of a quiet expiration for long enough to record six heart beats. Straining was carefully avoided and no significant changes have been attributable to the arrested breathing.

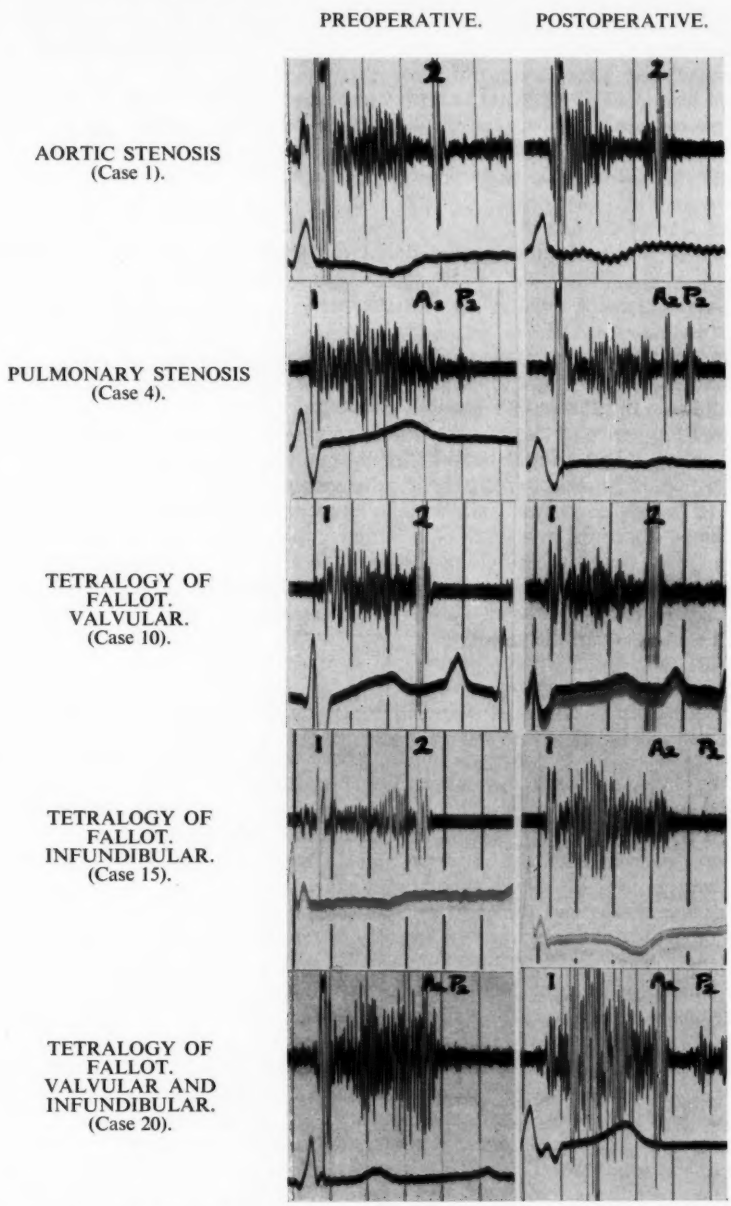


FIG. 1.—Phonocardiograms before and after operation. Upper tracings logarithmic (high frequency) phonocardiograms at the point of maximal intensity of the murmurs. Lower tracing: electrocardiogram lead II. Time lines 0·1 sec. (1) First heart sound. (2) Second heart sound. (A2) Aortic component of second heart sound. (P2) Pulmonary component of second heart sound.

In most cases the pressure gradient across the stenosis was measured at operation both before and after the valvotomy or infundibular resection. The gradients were measured by an electromanometer.

No attempt was made to assess the absolute intensity of the murmurs studied. This depends on the thickness of the tissues between the source of the murmur and the microphone, and is not proportional to the degree of stenosis. The following features were studied.

(1) The intervals between the beginning of the first heart sound and the beginning and end of the murmur.

(2) The duration of the murmur.

(3) The time of maximal intensity of the murmur (measured from the beginning of the first heart sound).

(4) The relationship of the end of the murmur to the pulmonary and aortic components of the second heart sound.

(5) The time interval between these components.

(6) The frequency of the vibrations constituting the murmur.

The beginning of the maximal vibrations of the first sound was considered to be the most reasonable time from which to measure the beginning and end of the systolic murmur and its point of maximal intensity. The interval between the pulmonary and aortic components of the second heart sound was similarly measured from the onset of the maximal vibrations of each. The frequency of the vibrations constituting the systolic murmur was measured by counting with a hand lens the number of vibrations in a tenth of a second. Slightly notched or slurred vibrations were counted as one. Only when the notching amounted to a change of direction were two vibrations counted. Such a system of counting vibrations naturally depends on the degree of amplification used in recording the sound tracings. This was kept reasonably constant by employing the same volume control setting for all the tracings.

Results

The most consistent change in the tracings following operation was that the frequency of the vibrations constituting the systolic murmur was lower (Table I). A reduction of frequency was present in nineteen cases, while in one case the frequency was unchanged. Indeed the pre-operative patients could be roughly distinguished from the post-operative ones on the basis of frequency. A frequency of 200 cycles per second or greater was present in seventeen patients before operation. A frequency of less than 200 cycles per second was present in eighteen patients after operation. There was no close correlation between the frequency and the pressure gradient across the stenosis. This may be partly because the phonocardiograms were taken at rest in bed whereas the gradients were measured under anæsthesia with the chest and pericardium opened.

The length of the systolic murmur was less closely related to the severity of the stenosis. The pre-operative length was greater in pure pulmonary stenosis than in the other conditions. The post-operative length was reduced by about a fifth in all cases in which the stenosis was valvular. In infundibular stenosis, however, the murmur was longer in three, the same in one, and slightly shorter in one.

The frequency in cycles per second multiplied by the length of the murmur gives the approximate total vibrations. The figures can be seen in the Table. The total vibrations gave a poorer indication of the severity of the stenosis than the frequency.

The time of onset of the murmur did not vary much. After operation ten started earlier, six were unchanged, and four started later. The time of ending of the murmur was much more interesting. Before operation the murmur ended late in all cases of pulmonary stenosis with normal aortic root. In these cases the murmur extended past the aortic component of the second heart sound. After operation the end of the murmur was earlier in all cases of valvular stenosis, but later in all cases of infundibular stenosis. The earlier ending of the murmur after valvotomy was sometimes such that the murmur stopped before the aortic component of the second heart sound.

The later ending after infundibular resection never extended past the aortic component of the second heart sound except in one case of acyanotic tetralogy of Fallot. In this case the murmur extended beyond the aortic component both before and after infundibular resection.

The time of maximal intensity of the murmur is conveniently termed the peak. This was late in pre-operative tracings and became earlier after operation in all cases except one. This was a case of tetralogy of Fallot with infundibular stenosis, and no change was found in the peak of the murmur. The peak followed the first heart sound by 0·15 seconds or more in thirteen out of twenty cases before operation. After operation it was less than 0·15 seconds after the first heart sound in seventeen cases.

The interval between the pulmonary and aortic components of the second heart sound could be measured in only 11 patients before operation. Six of these were patients with pulmonary stenosis and normal aortic root. In these the interval before operation appeared proportional to the pressure gradient found at operation. After operation the interval was reduced, and coincided roughly with the post-operative pressure gradient. There was a measurable interval between the aortic and pulmonary components of the second sound in only five of the eleven cases of tetralogy of Fallot before operation. In two patients with valvular stenosis the interval decreased after operation, while in two with infundibular stenosis and one with valvular and infundibular stenosis the interval increased. In a further three patients with tetralogy of Fallot a pulmonary component of the second heart sound was recorded only after operation—giving a measurable post-operative interval in eight of the eleven patients.

Discussion

The tracings were analysed to decide whether the character of the systolic murmur gave an indication of the degree of stenosis present. The various points of interest that have come to light during the study will be discussed later.

Can the severity of stenosis be assessed from the systolic murmur? This question will only be fully answered when established cases of idiopathic dilatation of the pulmonary artery and cases of mild pulmonary stenosis are analysed. The present series is only the first step towards the answer. It shows that there are changes in the systolic murmur after the relief of stenosis. The changes are such that the tracings before and after operation can usually be identified. The features involved are the frequency of the vibrations constituting the murmur and the time of maximal intensity of the murmur. When there is a normal aortic root there is the added factor that the gradient across the stenosed pulmonary valve can be assessed by the interval between the aortic and pulmonary components of the second heart sound.

The relationship of the frequency of the vibrations constituting a systolic murmur to the cause of the murmur has been discussed in a previous paper (Wells, 1957). The murmur of mitral regurgitation has often a frequency of over 200 cycles a second which represents a gradient of almost the whole ventricular pressure. The slight or moderate ejection murmurs which sometimes occur in a heart that is otherwise normal are considered innocent. These have a frequency of about 170 cycles a second. The coarse innocent murmurs are different from ejection murmurs in that they are briefer, occur earlier in systole, and have a frequency of about 110 cycles a second.

The earlier peak of intensity following valvotomy has not previously been described. Mannheimer and Jonsson (1954) have shown that in cases of pulmonary stenosis the murmur is earlier when the right ventricular pressure is below 70 mm. Hg. It is not unreasonable to relate the peak of intensity of the systolic murmur in aortic stenosis to the delay in the peak of aortic pressure. No doubt the same factors apply in pulmonary stenosis. It has been found that there is a relationship between the severity of aortic stenosis and the delay in the peak of aortic pressure (Dow, 1940; Goldberg *et al.*, 1954). The period of ejection is also longer in aortic stenosis (Bailey *et al.*, 1956). It is therefore possible that the length of a systolic murmur and the peak of its intensity will throw light on the period of ejection and the form of the arterial pulse.

Other Points of Interest Arising from the Present Study. Two of the eleven patients with tetralogy of Fallot were acyanotic at rest. In these the systolic murmur extended beyond the aortic component of the second heart sound. In none of the cyanotic cases did this occur. The diagnosis of tetralogy of Fallot was confirmed by the equal pressures in the ventricles and the free passage of a sound from the right ventricle to the aorta. The stenosis must clearly have been sufficiently mild for the pulmonary flow to be nearly as large as the aortic flow. Although one patient had valvular and the other infundibular stenosis, the auscultatory findings did not differ from pulmonary stenosis with a normal aortic root.

In the patients with tetralogy of Fallot the phonocardiograms did not show the differences described by Mannheimer and Jonsson (1954) that enable valvular stenosis to be differentiated from infundibular stenosis. The behaviour of those after infundibular resection did, however, differ from those after valvotomy. This supports their explanation of the early termination of the murmur in infundibular stenosis due to contraction in late systole of the infundibular region.

The pulmonary component of the second heart sound was recorded before operation in five of the eleven patients with tetralogy of Fallot and after operation in eight. This does not agree with the findings of Kjellberg *et al.* (1955), and Leatham and Weitzman (1956) who believe that the presence of a pulmonary component of the second heart sound is against the diagnosis of tetralogy of Fallot. From the present series it can be said that failure to record a pulmonary component of the second heart sound is more in favour of a diagnosis of Fallot's tetralogy than of pulmonary stenosis with a normal aortic root.

Summary

The systolic murmur was studied by phonocardiography in twenty patients before and after aortic or pulmonary valvotomy or infundibular resection.

The loudness of the murmur was not considered important and the significant changes were of the frequency of the vibrations and the timing of peak intensity. A frequency above 200 cycles per second and a peak later than 0·15 seconds after the first sound indicate severe stenosis.

In tetralogy of Fallot it was not possible to determine from pre-operative tracings whether the stenosis was valvular or infundibular. It was, however, found that valvotomy shortened the murmur while infundibular resection lengthened it.

A pulmonary component of the second sound was recorded in eight of eleven cases of tetralogy of Fallot. This component does not therefore establish the integrity of the aortic root.

Two patients with acyanotic tetralogy of Fallot had systolic murmurs that obscured the aortic component of the second heart sound. In none of the cyanotic cases did this occur.

I wish to thank Mr. O. S. Tubbs and Mr. I. M. Hill for permission to study their cases and for their continued encouragement and interest.

References

Bailey, C. P., Bolton, H. E., Nichols, H. T., Jannson, W. L., and Litwak, R. S. (1956). *J. Thor. Surg.*, **31**, 375.
Currens, J. H., Kinney, T. D., and White, P. D. (1945). *Amer. Heart J.*, **30**, 491.
Donzelot, E., and D'Allaines, F. (1954). *Traité des Cardiopathies Congenitales.* 1st ed., Paris, p. 235.
Dow, P. (1940). *Amer. J. Physiol.*, **131**, 432.
Dow, J. W., Levine, H. D., Elkin, M., Haynes, F. W., Hellems, H. K., Whittenberger, J. W., Ferris, B. G., and Goodale, W. T. (1950). *Circulation*, **1**, 267.
Downing, D. F. (1956). *Circulation*, **14**, 188.
Goldberg, H., Bakst, A. A., and Bailey, C. P. (1954). *Amer. Heart J.*, **47**, 527.
Greene, D. G., Baldwin, E. de F., Baldwin, J. S., Himmelstein, A., Roh, C. E., and Cournand, A. (1949). *Amer. J. Med.*, **6**, 24.
Kjellberg, S. R., Mannheimer, E., Rudhe, U., and Jonsson, B. (1955). *Diagnosis of Congenital Heart Disease.* 1st ed. Chicago, p. 143.
Leatham, A., and Weitzman, D. (1956). Second European Congress of Cardiology. Stockholm.
Mannheimer, E., and Jonsson, B. (1954). *Acta pediat.* Supp. 100, p. 167.
Ordway, N. K., Levy, L., Hyman, A. L., and Bagnetto, R. L. (1950). *Amer. Heart J.*, **40**, 471.
Reinhold, J. D. N., and Nadas, A. S. (1954). *Amer. Heart J.*, **47**, 405.
Vogelpoel, L., and Schrire, V. (1955). *Circulation*, **11**, 714.
Wells, B. G., Rappaport, M. B., and Sprague, H. B. (1949). *Amer. Heart J.*, **37**, 586.
—— (1957). *Brit. Heart J.*, **19**, 129.

PULMONARY HYPERTENSION IN CONGENITAL HEART DISEASE

BY

WILLIAM EVANS and D. S. SHORT

From the Cardiac Department of the London Hospital

Received February 10, 1958

An important group of congenital cardiovascular defects is that characterized by the presence of an arterio-venous shunt, of which atrial septal defect, ventricular septal defect, and patent ductus arteriosus are common examples. In these the flow of blood is generally directed from left to right so that cyanosis is absent, but some may ultimately develop cyanosis (cyanose tardive) following a reversal of the shunt. Cardiac catheterization may then show the pressure in the pulmonary artery to be raised to the same level as that in the aorta.

Ligature of a patent ductus is a safe procedure and the surgical treatment of atrial and ventricular septal defect is becoming established practice. The need now is to recognize in these cases the advent of pulmonary hypertension due to obstructive pulmonary vascular disease, for closure of the fistula in this circumstance cannot be curative.

Although close attention has been paid to the pathology of pulmonary hypertension associated with congenital heart disease in recent years, there is need for further investigation into the mechanism of the hypertension, and a readier recognition of the particular congenital lesion associated with it. In previous papers we described pulmonary hypertension as a solitary finding (Evans *et al.*, 1957), and again in association with mitral stenosis (Evans and Short, 1957). In this paper we deal with it in conjunction with congenital cardiovascular disease. Although such a combination is not rare in clinical practice, we have elected to describe here only the 11 cases that were ultimately examined at necropsy.

As in our two previous series of patients a diagnosis of pulmonary hypertension was made from a clinical, electrocardiographic, and radiological examination, and independent of cardiac catheterization which was carried out in some of the patients. Thus, we have defined pulmonary hypertension as *a persistent rise of pulmonary arterial pressure sufficient to cause enlargement and ultimately failure of the right ventricle, with characteristic clinical, electrocardiographic and radiological signs.* A perusal of the growing number of reports of pulmonary hypertension has convinced us of the need to adhere to this definition. The acceptance of pulmonary arterial pressure readings as the sole arbiter of pulmonary hypertension, irrespective of evidence of right ventricular hypertrophy, will lead inevitably to the confusion now commonplace in the diagnosis of systemic hypertension when deduced exclusively from manometric readings from the arm. In cases of congenital heart disease with left-to-right shunt the pulmonary arterial pressure is frequently raised, but in only a proportion of these is there true pulmonary hypertension. This distinction is imperative for the proper management of the patients.

The 11 cases that we describe are arranged in four groups according to the kind of congenital anomaly found in association with pulmonary hypertension. Thus, there were three patients with atrial septal defect, three with ventricular septal defect, four with patent ductus arteriosus, and one with a common aorto-pulmonary trunk. Pulmonary arteriography was carried out at necropsy in four of the cases. In the others the test could not be performed because the patient had died suddenly either at home or at another hospital. Blocks were taken for histological examination in every

case. In Case 10, only two blocks were made available, but in the others between 4 and 18 blocks were removed. These were examined after staining with either Hart or Verhoeff elastic stain.

In the sections that follow we first present the clinical and pathological findings in each patient, and subsequently the effects that pulmonary hypertension and the particular congenital anomaly may have on one another. Finally, we consider the pathology and pathogenesis of the hypertension in relation to the congenital cardiovascular defects as a group.

Pulmonary Hypertension in Atrial Septal Defect

Case Reports

Glossary of Abbreviations: BP=Blood pressure. MCL=Mid-clavicular line. AAL=Anterior axillary line. SVC=Superior vena cava. RA=Right atrium. RV=Right ventricle. LV=Left ventricle. LA=Left atrium. PA=Pulmonary artery. RUL and RLL=Right upper and lower lobes. LUL and LLL=Left upper and lower lobes. EC=Electrocardiogram. PAP=Pulmonary artery pressure. PCP=Pulmonary capillary pressure. RBC=Red blood cells in millions per c. mm. WBC=White blood cells in thousands per c. mm. Hb=Hæmoglobin expressed as percentage. WR=Wassermann reaction. Wt=Weight. FOC=Foramen ovale closed. FOP=Foramen ovale patent.

Case 1. S. S., aged 52, a married woman without children. No symptoms until 36, when she started attacks of paroxysmal tachycardia. At the age of 49 one attack lasted a fortnight, and she was admitted to hospital with congestive heart failure.

Examination. During the paroxysm, the patient was dyspnœic and cyanosed, with jugular venous engorgement and slight œdema. BP 120/80. After sinus rhythm had been restored she remained cyanosed. No clubbing of fingers. The apex beat was just outside the MCL, and there was a systolic thrill and murmur. A single second sound was followed by a Graham Steell murmur. RBC, 6·64. Hb, 126. Arterial oxygen, 67%.

Radiology. Great enlargement of RA and of PA which bulged. PA branches dilated and abnormally pulsatile. Clear peripheral lung fields. Pulmonary hilar clouding latterly.

EC. At different times the tracing showed normal rhythm, extrasystoles, auricular tachycardia, auricular fibrillation, and auricular standstill. S wave deep in I and CR7, and absent in CR1 where R was very tall. T wave inverted in leads II, III, and in CR1 to CR4. P wave diphasic in CR1. Partial right bundle-branch block pattern.

Course. Progressive dyspnœa on effort and œdema of the ankles. A year later she had two pulmonary emboli in quick succession and died suddenly.

Necropsy. Customary changes of heart failure in viscera. No thrombosis in heart or in pelvic or femoral veins.

Heart. Wt 650 g. Great dilatation and hypertrophy of RA and RV (0·9 cm. thick). LV normal (1·1 cm. thick). Slight thickening of aortic cusp of mitral valve. Defect (3 cm. diam.) in posterior part of atrial septum.

Lungs. Recent hæmorrhagic infarcts of right middle and lower lobes. PA trunk, right, left, and segmental branches dilated and bearing numerous flecks of atheroma. Organizing thrombus in right pulmonary artery and its middle and lower lobe branches. Pulmonary arteriography showed left pulmonary artery and segmental branches to be enormously dilated. Lobular arteries ended abruptly and the finest branches were lost throughout most of lung, but peripheral pattern normal in some parts. Subpleural inter-pulmonary arterial anastomoses visible in several places.

Microscopy. Elastic arteries showed atherosclerosis and organizing thrombosis. Muscular arteries showed widespread occlusive disease, especially vessels with a diameter below 0·5 mm. Process sometimes thrombotic, but elsewhere intimal proliferation was non-specific. Focal or diffuse attenuation of media was frequent in such stenosed or occluded arteries, some of them appearing as mere ghosts. Similar changes were present in arterioles. Abundant collateral channels. Bronchial arteries more numerous than usual. Venules showed moderate subendothelial thickening. One pulmonary infarct present.

Case 2. I. Y., aged 33, was a married woman without children. She had suffered from dyspnœa and cyanosis on effort since birth and attacks of palpitation latterly. During an attack of chorea at the age of 7, a pulmonary systolic murmur was discovered. At the age of 24 she developed cardiac pain on effort, and shortly afterwards started having small hæmoptyses. At the age of 30, attacks of nocturnal dyspnœa commenced and she was unable to lie flat when she was admitted to hospital.

Examination. No definite cyanosis and no clubbing. Pulse normal; rhythm regular. BP 105/65. Jugular pulse normal. No œdema. Right ventricular systolic lift. Early systolic sound audible in all areas. Systolic murmurs at tricuspid and pulmonary areas. Close splitting of the second sound with loud pulmonary element, followed by Graham Steell murmur. Hb, 125. RBC, 6·15.

Radiology. Considerable enlargement of RA, and gross dilation of PA and its branches. Clear peripheral lung fields.

EC. Extrasystoles and auricular tachycardia on occasions. S wave very deep in leads I and CR7, and absent in CR1 where R was very tall. T wave inverted in III and in CR1, but upright in CR4. P diphasic in CR1.

Cardiac Catheterization. PAP 100/50 mm. Hg. Systemic flow 2·5 litres/min.; pulmonary flow 3·3 litres/min.

Course. She developed a cough, severe hæmoptysis, and pleuritic left chest pain, and died a fortnight later.

Necropsy. Customary changes of heart failure in viscera. No thrombosis in heart or in pelvic or femoral veins.

Heart. Wt 645 g. Great hypertrophy of RV (1·5 cm. thick). LV 1·6 cm. thick. RA moderately dilated and hypertrophied. Atrial septal defect large enough to admit forefinger, immediately below entrance of SVC. Abnormal venous drainage of right lung, upper and middle veins entering SVC. FOC.

Lungs. Left pleural cavity half full of blood-stained effusion. Recent large infarction of LLL. Pulmonary trunk and main branches dilated. Left pulmonary artery occluded by mass of recent thrombus.

Microscopy. Elastic arteries, showing old and recent thrombus, greatly narrowed in places. Widespread narrowing or occlusion of small muscular arteries by elastoid intimal proliferation, and sometimes thrombosis with canalization. Focal hypoplasia of media was a frequent finding. Disintegration of many small muscular arteries gave to them a ghost-like appearance. Adjacent to many of the obstructed arteries were thin-walled collateral vessels often containing organized thrombus. Arterioles frequently either partially or wholly occluded by intimal proliferation. Bronchial arteries and venules normal.

Case 3. P. A., a single woman, aged 32, was first seen at 27. She had ill-defined rheumatism as a child. A heart murmur was noted at the age of 5 and restriction of activity was advised. In spite of this she was able to skate and dance a little up to the age of 24. At 27, she became very breathless after climbing two flights of stairs, and also had attacks of palpitation with sudden onset from childhood and more severe during past five years. When 29, she had an attack of palpitation lasting several days and leading to cardiac pain and to unconsciousness, for which she was admitted to hospital.

Examination. Cyanosis, but no finger clubbing. Strawberry nævus on left cheek. Pulse small and irregular from extrasystoles; once auricular tachycardia. BP 110/75. Prominent *a* wave in jugular veins. Apex beat in AAL. Striking systolic lift over right ventricle. Systolic thrill over pulmonary artery, second sound closely split, and its pulmonary element accentuated. First sound increased at apex and short mid-diastolic murmur heard. No œdema. Hb, 90.

Radiology. Great enlargement of RA, RV, and especially of PA which bulged. Right and left branches dilated and abnormally pulsatile. Clear peripheral lung fields. Aortic knuckle small.

EC. S wave very deep in leads I and CR7, and absent in CR1 where R was tall. S–T segment depressed in leads II, III, and CR4 and T wave inverted in CR1. P waves not abnormal.

Catheterization. PAP 60/25 mm. Hg. Systemic flow 4 litres/min.; pulmonary flow 11·5 litres/min. Pulmonary vascular resistance approximately 3 units.

Course. Because her effort tolerance had decreased steadily during the past three years, surgical closure of the septal defect was advised and the patient was re-admitted to hospital. Catheterization then showed a right ventricular systolic pressure of 75 mm. Hg, a systemic flow of 2·75 litres/min., and a pulmonary flow nearly twice as great. The pulmonary vascular resistance had risen to about 10 units. The patient died from intractable ventricular fibrillation the day after the defect had been closed.

Necropsy. Moderate congestion of viscera. No thrombosis in heart or in systemic veins.

Heart. Wt 505 g. Sutured atrial septal defect 3 cm. long. Mitral stenosis, admitting one finger with difficulty. Great hypertrophy and dilatation of RV (0·9 cm. thick) and RA. Hypertrophy of LA. LV small (1·4 cm. thick).

Lungs. PA greatly dilated (9·0 cm. circumference; aorta, 5·5 cm.) showing numerous flecks of atheroma, but no thrombosis or infarction. Pulmonary arteriography showed left pulmonary artery and segmental branches to be greatly dilated, but lobular arteries smaller than normal and finest branches lost throughout. One small infarct.

Microscopy. Flecks of atheroma in elastic arteries. Great majority of muscular arteries less than 0·2 mm. diam., narrowed or occluded by elastoid intimal proliferation. Focal or diffuse medial thinning frequently present in these vessels. Many muscular arteries contracted, some being as small as 0·04 mm. in diameter. Many arterioles narrowed by intimal proliferation. Endothelial thickening conspicuous in venules. Bronchial arteries normal.

Incidence

Bedford *et al.* (1957) diagnosed obstructive pulmonary hypertension in 15 of their 100 cases of atrial septal defect, and Campbell *et al.* (1957) found a high pulmonary vascular resistance in 20 per cent of their 46 cases investigated by cardiac catheterization. These figures agree closely with those of Wood (1956) who found extreme pulmonary hypertension in 16 per cent of his cases with an atrial septal defect large enough to permit a pulmonary flow three times as great as the systemic flow.

In Wood's series, an average age of 22 years in those with a high pulmonary vascular resistance was similar to that in cases of uncomplicated atrial septal defect, namely 23 years, but in both Bedford's and Campbell's series, the patients with pulmonary hypertension tended to be older. Thus, in Bedford's series, 62 per cent were under 30, but only 6 of the 15 with pulmonary hypertension; 3 of the 15 were between 30 and 40 years, and 6 were over 40. Similarly, in Campbell's series 67 per cent were under 30, but only 2 of his 9 cases of pulmonary hypertension were in this group; the ages of the remaining 7 were between 33 and 52. Our three cases were aged 32, 33, and 52 years at death. It would seem, therefore, that pulmonary hypertension in atrial septal defect rarely proves fatal before the age of 25 years.

There are no reliable data concerning the sex incidence of pulmonary hypertension in association with atrial septal defect. In uncomplicated cases the female to male ratio is approximately 2·5 to 1 (Bedford *et al.*, 1957; Campbell *et al.*, 1957). Our three patients were women.

Clinical Features

These simulated those found in solitary pulmonary hypertension (Evans *et al.*, 1957), and included dyspnœa, cardiac pain, syncope, cyanosis, a small pulse, low blood pressure, a prominent atrial pulse in the neck, increased right ventricular pulsation, close splitting of the second heart sound with accentuation of its pulmonary component, and a Graham Steell murmur of pulmonary incompetence. A variation in some of these signs caused by the septal defect, however, requires special mention.

Palpitation was a prominent symptom in each of our three patients; extrasystoles and auricular tachycardia were present in all, and in one auricular fibrillation and auricular standstill had also taken place. When arrhythmia is a prominent feature in pulmonary hypertension, and when mitral stenosis is absent, it suggests the presence of atrial septal defect. Cyanosis was conspicuous in two of the three and appeared on effort in the third. Finger clubbing was absent even in the patient in whom cyanosis was alleged to have been present from birth.

Outward displacement of the apex beat as far as the anterior axillary line was a noticeable feature in all three cases. Such a degree of cardiac enlargement is unusual in pulmonary hypertension, so that its presence suggests an associated atrial septal defect. Conspicuous enlargement of the pulmonary artery also suggested the diagnosis of atrial septal defect in our cases known to have pulmonary hypertension. Such a change gave prominence to other physical signs, namely, visible and palpable pulsation over the pulmonary artery, a systolic thrill, a diastolic shock, a loud and often rough systolic murmur, and an obvious Graham Steell murmur.

The Electrocardiogram. The QRS complex in the right pectoral lead is abnormal in the majority of patients with atrial septal defect (Barber *et al.*, 1950; Bedford *et al.*, 1957). Although the deformity has usually been referred to as incomplete or complete right bundle-branch block, Taimont *et al.* (1952) believed that when the QRS did not exceed 0·1 sec. it was evidence of right heart hypertrophy, while Walker *et al.* (1956) believed that the secondary R wave of the curve was the result of selective hypertrophy of the basal portion of the right ventricle. Campbell *et al.* (1957) have advised that the terms incomplete bundle-branch block should be abandoned when describing the cardiogram of atrial septal defect, and proposed that direct reference should be made to the presence of primary and secondary R waves, and to the width of the QRS complex.

Wagner and Graham (1957) found that there was always cardiographic evidence of right ventricular hypertrophy when the pulmonary artery pressure was high, and that it was often present in patients whose pressure was normal. It appeared to them that "increased flow hypertrophy" was indistinguishable from "pressure hypertrophy."

It is clearly important to determine whether true pulmonary hypertension, as defined in this paper, due to obstruction within the lesser pulmonary arteries, can be recognized from the cardiogram. We, therefore, examined the tracing in 50 adult patients with this congenital anomaly, and found three distinctive patterns in each of the two groups.

Thus, in *uncomplicated* atrial septal defect (Fig. 1), the *first* pattern consisted of a deep S wave in leads I and CR7, an R wave greater or slightly less than S in CR1 where the T wave was inverted, and no widening of the QRS period. In the *second* pattern the QRS period was widened to 0·1 sec., and an RSR′ type of curve appeared in CR1. The *third* pattern was similar to the former except that a RSR′S′ complex appeared in CR1. A slight variant of this curve appeared in three instances (Fig. 3). It so happened that complete right bundle-branch block with a QRS measuring at least 0·12 sec. was not met with in this group, nor was a qRS pattern in either group.

When the atrial septal defect was associated with *pulmonary hypertension* there were also three distinctive cardiograms (Fig. 2). In the *first* pattern there was lengthening of the QRS period to 0·1 sec.; in CR1 the R was tall and the S wave correspondingly short, while the T wave was inverted or depressed in this lead and in leads to the left as far as CR4; the T was also inverted in leads III and IIIR and somewhat depressed in lead II. It is these features that indicate conclusively the presence of pulmonary hypertension in atrial septal defect. Bedford (1957) has found the same criteria to apply in his patients. In the *second* pattern, in addition to the changes just described, a

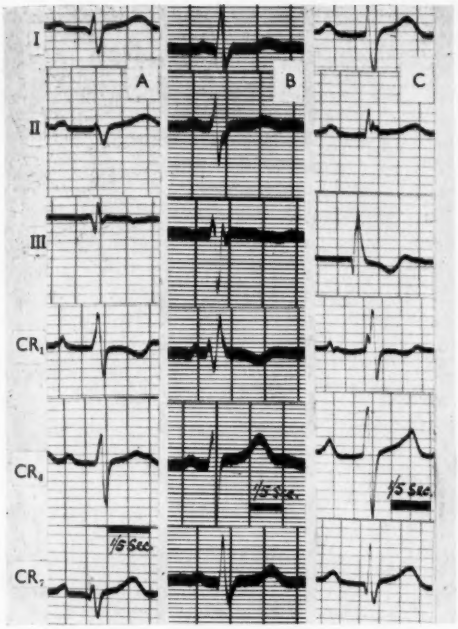


FIG. 1.—*Uncomplicated Atrial Septal Defect.* Three common electrocardiographic patterns. (A) Deep S wave in leads I and CR7, an R wave greater than S in CR1 where T is inverted, and no widening of QRS complex. (B) Widening of QRS to 0·1 sec., with an RSR′ pattern in CR1. (C) Similar to (B) except for an RSR′S′ complex in CR1.

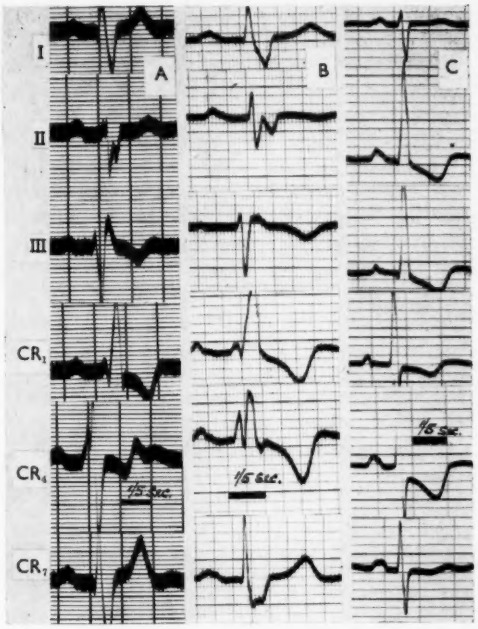


FIG. 2.—*Atrial Septal Defect and Pulmonary Hypertension.* Three common electrocardiographic patterns. (A) Lengthening of QRS period, tall R in CR1 with inversion or depression of T wave in this lead and in leads as far to the left as CR4; T is also inverted in leads III and IIIR (not shown), and depressed in II. (B) Similar to (A) with the addition of greater widening of QRS to 0·15 sec., constituting bundle-branch block. (C) Similar to (A) except that there is no widening of QRS which shows an RS pattern in CR1.

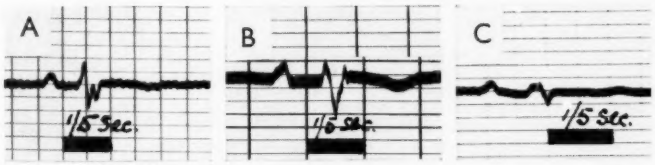


FIG. 3.—*Uncomplicated Atrial Septal Defect.* Three less common patterns of QRS complex in CR1.

characteristic curve of complete right bundle-branch block with its wide QRS period of 0·12 sec. or over, was present. In the *third* pattern the changes were identical with those in the first except that the QRS period was of normal length with an RS design in CR1.

Auricular arrhythmia was present in five patients with pulmonary hypertension and in one without. This finding, therefore, especially in a young patient with atrial septal defect, suggests

the presence of pulmonary hypertension, and in one with hypertension it points to the association of atrial septal defect unless mitral stenosis is present.

Radiology. There is great enlargement of the pulmonary artery and its primary branches which on screening are seen to pulsate excessively unless occluded by thrombus, as sometimes happens. The periphery of the lung fields is clear. There is considerable enlargement of the right atrium and ventricle. The aortic knuckle is either small or hidden by the distended pulmonary artery (Fig. 7).

Cardiac catheterization in two of our patients established the diagnosis of atrial septal defect with pulmonary hypertension, but this test was considered to be an unjustifiable risk in the third, as indeed it is in many patients with severe pulmonary hypertension.

Treatment. In our view the surgical closure of atrial septal defect when complicated by pulmonary hypertension, as defined in this paper, is never justified. Not only is the procedure hazardous, but in view of the obstructive lesions that abound in the lesser pulmonary arteries, it can never do good. This opinion is shared by Bedford *et al.* (1957) who state that pulmonary hypertension of the hyperkinetic type, due to a large flow and not to a seriously raised vascular resistance, is no contra-indication to surgical treatment, but that obstructive pulmonary hypertension is another matter. Moreover, they opine that even when the shunt is from left to right, closure of an atrial septal defect in the presence of severe pulmonary vascular disease removes the safety-valve action of a potential right-to-left shunt during exertion and so virtually enhances the hypertension.

Pulmonary Hypertension in Ventricular Septal Defect

Case Reports

Case 4. J. L., a single woman, aged 30, was first seen when 28. She had always been somewhat short of breath.

Examination. No cyanosis or clubbing. Pulse normal. BP 120/70. Apex beat just outside MCL. Palpable impulse and systolic thrill over a wide area to the left of the sternum. Rough and long systolic murmur heard in all areas and especially loud in the fourth left intercostal space. Second sound rather loud and apparently single, immediately followed by a moderately rough early diastolic murmur. A murmur in mid-diastole was audible in the mitral area. Hb, 85. RBC, 5.

Radiology. Moderate enlargement of RA and RV. Considerable enlargement of PA and of its branches which showed increased pulsation. Clear peripheral lung fields.

EC. Sinus rhythm. S wave very deep in leads I and CR7 and absent in CR1. T wave upright in leads II and III, inverted in CR1 and depressed in CR4. S–T depressed in I and R very tall in CR7. P wave inverted in leads II, III, CR4, and CR7, and very tall and spiky in CR1.

Course. Two years later, attacks of unconsciousness were followed by retrosternal pain. Signs unchanged. Four weeks later, the patient died suddenly in a train.

Necropsy. Customary changes of heart failure in viscera. No thrombosis in heart or in systemic veins.

Heart. Wt 575 g. Great hypertrophy of RV (1·1 cm. thick). Moderate hypertrophy of LV (1·8 cm. thick). Defect (1·8 cm. diameter) in the membranous portion of the interventricular septum. PFO (valvular). Fenestration of aortic cusps.

Lungs. PA showed scanty atheroma. Several small branches filled with recent thrombus.

Microscopy. Elastic arteries normal. Muscular arteries showed a remarkable degree of contracture, the larger ones presenting thick media and prominent internal elastic lamina. Many smaller muscular arteries were of arteriolar size, some having a diameter of only 0·04 mm. Intimal proliferation present in a few muscular arteries with segmental hypoplasia of media. Many arterioles showed pallisading of endothelial nuclei around narrowed lumen. Bronchial arteries normal.

Case 5. A. M., aged 20, was admitted to hospital with a staphylococcal pyæmia. Although he had been blue from birth, he had suffered no great disability and was able to work as a clerk until his recent illness.

Examination. Obvious cyanosis and some clubbing of fingers. Pulse small. BP 110/80. No œdema. Apex beat in AAL. Systolic murmur and loud Graham Steell murmur at left sternal border. Hb, 100.

Radiology. Moderate enlargement of RA and RV. Great enlargement of PA and its branches traceable almost to the periphery of the lungs. Some hilar clouding.

Course. The patient died from pyæmia after an illness lasting 5 days. An electrocardiogram was not recorded.

Necropsy. Customary changes of heart failure and of septicæmia in viscera. Numerous miliary pyæmic abscesses in liver. No thrombosis in heart or in systemic veins.

Heart. Wt 640 g. Great hypertrophy of RV (0·7 cm. thick), and considerable hypertrophy of LV (2·0 cm. thick). Defect (3·5 cm. diam.) in membranous part of interventricular septum. The aorta which was hypoplastic, arose mainly from the RV. The PA arose equally from both ventricles. FOC.

Lungs. Great dilatation of pulmonary trunk (11 cm. circumference; aorta 5·5 cm.) and its branches. Scanty atheroma in these vessels, but numerous patches in the intrapulmonary arteries.

Microscopy. Elastic arteries showed moderate atherosclerosis. Muscular arteries, especially vessels with a diameter below 0·6 mm. diameter, partly or wholly occluded by intimal proliferation which lay adjacent to areas of

hypoplasia and aplasia of media. Thrombosis with re-canalization of some muscular arteries. Arterioles showed similar, though less severe changes. Bronchial arteries and venules normal.

Case 6. L. P., a man, aged 36, had been blue for as long as he could recall. A heart lesion had been discovered at the age of two years. He had never been able to run, and was breathless on hills. When 31, he was admitted to hospital for investigation. His symptoms had not increased since the age of 15, and during this time he had suffered from recurrent cough, bronchitis, and hæmoptysis.

Examination. There was moderate cyanosis and clubbing of fingers. The pulse was natural. BP, 150/90. Jugular venous pulse and pressure normal. Systolic lift over RV. Palpable diastolic shock and thrill to left of sternum. Pansystolic murmur, audible all over præcordium, maximal in fourth left intercostal space. Second sound in pulmonary area loud and single, though splitting was just detected on deep inspiration. Graham Steell murmur heard once. Hb, 150; RBC, 6·6. Cardiac catheterization showed a high PAP 130/64 mm. Oxygen saturation, femoral artery, 89 per cent.

Radiology. Moderate enlargement of heart to right and left. Similar enlargement of PA and its primary branches which pulsated obviously. Lung fields normal. Angiocardiography showed early filling of a normal sized aorta.

EC. Deep S wave in leads I and CR7. T low in II, inverted in III and in CR1 where R was tall and S absent.

Course. Hæmoptysis recurred, but without general deterioration until the age of 35 when cyanosis and breathlessness increased and intermittent claudication set in. He was admitted with symptoms of pulmonary infarction. Five days later, he collapsed while sitting on a bedpan and died suddenly.

Necropsy. Congestion of viscera. No thrombosis of heart or systemic veins.

Heart. Wt 700 g. Great hypertrophy of RV. Small atrial septal defect. Aorta, over-riding the ventricular septal defect, was 2·5 cm. diameter at its commencement, gradually tapering to 1·0 cm. diameter, but without coarctation.

Lungs. PA greatly dilated with flecks of atheroma. Recent infarct in LLL.

Microscopy. Elastic arteries showed occasional plaques of atherosclerosis and recent thrombosis. Large muscular arteries frequently abnormal, showing aplasia of the media, with overlying intimal proliferation or organizing thrombosis, and involving either a segment of an artery or its entire circumference. Adjacent to many of these arteries were thin-walled collateral vessels, some of them containing organized thrombus. Majority of small muscular arteries greatly narrowed by thrombus. In these arteries the internal elastic lamina was exceptionally thick and overlaid with intimal proliferation which mainly consisted of layers of elastic fibres. Disintegration of many small muscular arteries gave to them a ghost-like appearance. Arterioles partially or wholly occluded by intimal proliferation. Bronchial arteries and venules normal.

Incidence

The incidence of pulmonary hypertension in ventricular septal defect is difficult to determine, partly because the isolated fistula is not so common as was thought, and partly because of the confusion arising from the use of the term, Eisenmenger complex. In this paper a case where the aorta over-rode the right ventricle is not kept apart from cases of septal defect with pulmonary hypertension in whom the aortic root was normal. Wood *et al.* (1954) found severe hypertension in 24 per cent of their cases of isolated septal defect, but the incidence rises to 57 per cent if cases with a defect less than 1 cm. in diameter are excluded (Wood, 1956).

Wood found the average age of uncomplicated ventricular septal defect to be 13 years compared with 22 years for those with pulmonary hypertension. On the other hand, among 20 patients with hypertension reported by DuShane *et al.* (1956), 19 were children under 12 years of age. Three of the six patients reported by Brown *et al.* (1955) were also aged 16 year or under. Selzer and Laqueur (1951) reviewed 35 cases of Eisenmenger complex examined at necropsy and found that the majority died in the third or fourth decade, although three had survived beyond the age of 50. Our three patients died at the age of 20, 30, and 36 years respectively.

The sex incidence appears to be the same whether pulmonary hypertension is present or absent. In the isolated fistula, male and female patients are equally affected. In the series with hypertension reported by Selzer and Laqueur (1951) 55 per cent were male. Two of our patients were men and one a woman.

Clinical Features

Cyanosis is often slight. Thus, it was absent in four cases described by Espino-Vela and Mata (1956) and inconspicuous in the six patients reported by Brown *et al.* (1955). It was absent in one of our patients, but obvious in the other two and associated with clubbing of fingers.

The pulse is not necessarily small in pulmonary hypertension associated with ventricular septal

defect. The pansystolic murmur, characteristic of lone ventricular septal defect tends to shorten into a mid-systolic murmur with the advent of pulmonary hypertension (Fig. 4), and in four of the six cases reported by Brown *et al.* (1955) the systolic murmur was absent. A pansystolic murmur accompanied by a thrill was, however, present in two of our cases, but in the third the murmur was shorter and softer. A Graham Steell murmur was present in two cases.

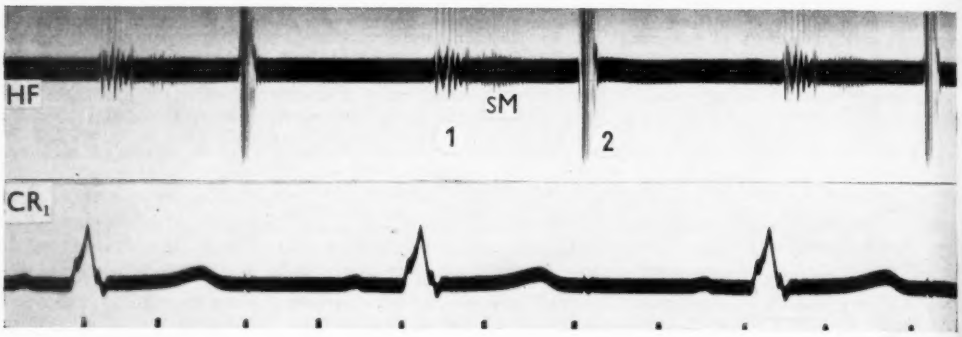


FIG. 4.—*Ventricular Septal Defect and Pulmonary Hypertension.* Attenuated murmur limited to mid-systole.

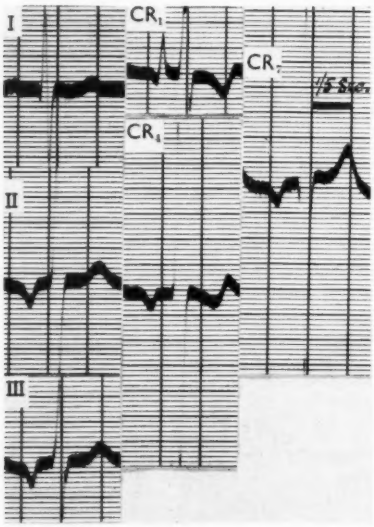


FIG. 5.—*Ventricular Septal Defect and Pulmonary Hypertension.* Tall R and very tall P with inversion of T in CR1, and S–T depression in CR4, indicate hypertrophy of RA and RV. S–T distortion in I and Q and very tall R waves in CR7 suggest associated left ventricular hypertrophy. Case 4.

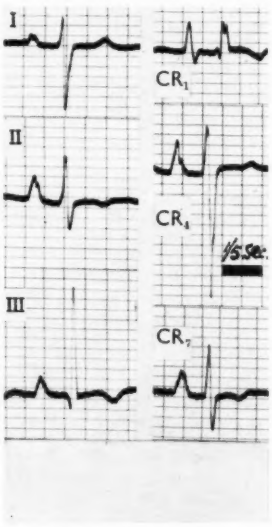


FIG. 6.—*Patent Ductus Arteriosus and Pulmonary Hypertension.* S–T depression in CR7 suggests left ventricular hypertrophy. Other changes typify right atrial and right ventricular hypertrophy. Case 9.

The Electrocardiogram. In uncomplicated ventricular septal defect the tracing is normal when the shunt is small, and often when it is of moderate size. When the shunt is large, evidence of enlargement of both ventricles may appear. Thus, a secondary R wave may appear in right-sided leads, and a Q wave followed by a tall R wave in left-sided leads (Wood *et al.*, 1954). In the presence of pulmonary hypertension the cardiogram shows mainly right heart preponderance, but as happened in one of our three cases there is sometimes evidence of left ventricular hypertrophy (Fig. 5).

Radiology. According to Brown *et al.* (1955) radiological examination of the heart shows that the pulmonary artery is not as large when pulmonary hypertension complicates ventricular septal defect as in the case of atrial septal defect. Campbell (1951), on the other hand, found very large pulmonary arteries in this anomaly. Our three patients showed moderate enlargement of the heart and similar or greater enlargement of the pulmonary arterial trunk and its main branches (Fig. 8 and 9).

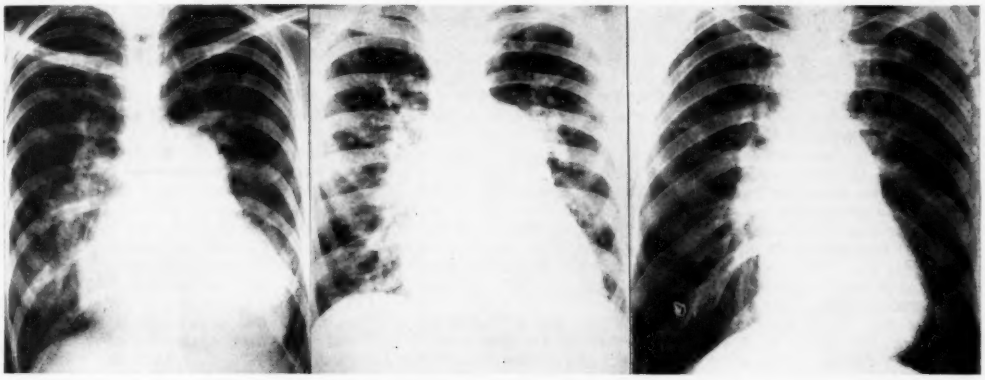


FIG. 7.—*Atrial Septal Defect and Pulmonary Hypertension.* Great enlargement of PA and its branches. Periphery of lung fields clear. Considerable enlargement of RA and RV. Case 3.

FIG. 8.—*Ventricular Septal Defect and Pulmonary Hypertension.* Moderate enlargement of RA and LV. Great enlargement of PA and its branches which are seen as far as the periphery. Case 5.

FIG. 9.—*Ventricular Septal Defect and Pulmonary Hypertension.* Apparent prominence of LV. Enlargement of RV in left oblique. Moderate enlargement of PA and its primary branches. Lung fields normal. Case 6.

Cardiac catheterization was performed in one of our cases, but the investigation afforded no evidence of the site of the shunt, and the test has a limited value, in addition to carrying some risk, in these patients. Similarly, *angiocardiography* is not invariably helpful (Campbell and Hudson, 1951).

PULMONARY HYPERTENSION IN PATENT DUCTUS ARTERIOSUS

Case Reports

Case 7. I. W., a single woman aged 22, was born with Madelung's deformity with absence of both radii and thumbs. She was otherwise well until the age of 14 when she became breathless on effort and developed a productive cough. At the age of 18 the dyspnœa and cough were worse and a year later she attended hospital.

Examination. Slight cyanosis, but no clubbing. Pulse small. BP 110/80. Split second sound with loud pulmonary element. Graham Steell murmur. Triple rhythm due to addition of the third heart sound.

Radiology. Slight enlargement of RA, considerable enlargement of RV and of pulmonary trunk. Right and left PA and their branches dilated and pulsatile. Peripheral lung fields normal.

EC. S wave very deep in lead I, and small in CR1 where R was very tall. S–T depressed in II and T wave inverted in leads III and CR1. P wave tall in II and tall and spiky in CR1.

Course. At the age of 21, œdema appeared and persisted in spite of mercurial injections, and she was later admitted to hospital with dyspnœa, cough, œdema, and hoarseness. Cyanosis was then evident and the pulse was small. BP 105/80. The liver edge was just felt and there was gross œdema of the legs and thighs. Hb, 125. RBC, 11·2. Her condition continued to deteriorate, with severe attacks of dyspnœa and increasing cyanosis. She developed pulmonary infarction and died a fortnight later.

Necropsy. Customary changes of heart failure in viscera. No thrombosis in systemic veins. Other congenital malformations apart from the heart and Madelung's deformity included absence of left uterine cornu and left Fallopian tube; left kidney lay just above right pelvic brim and was somewhat mis-shapen.

Heart. Very great hypertrophy, without dilatation of RV (1·4 cm. thick). LV normal. RA greatly dilated. RA and RV contained loosely-attached thrombus. Slight fibrous thickening of pulmonary valve cusps. FOC. Ductus arteriosus (0·9 cm. diameter). Descending aorta and left PA contiguous at site of fistula.

Lungs. Hæmorrhagic infarction of entire RUL. PA trunk greatly dilated. (PA 7·5 cm. circumference; aorta 5·5 cm.). Severe atheroma in both large and small branches of PA. Artery to RUL occluded by embolus.

Microscopy. Extensive atherosclerosis in elastic arteries. Muscular arteries showed very widespread occlusive changes, with hardly a normal muscular artery to be seen. Breaks in walls of muscular arteries in places with external herniation of reactive fibrous tissue. Hypoplasia and sometimes aplasia of media adjacent to occlusive intimal proliferation. Abundant collateral channels, especially in vicinity of occluded arteries. Majority of arterioles occluded by intimal proliferation similar to that in muscular arteries. Bronchial arteries prolific. Venules normal.

Case 8. A. B., married woman, aged 24, said to have had heart disease from birth. While at school she could not play games because of shortness of breath, throbbing in the neck, and aching in the gums. She became cyanosed when cold, and suffered from a cough every winter. When 17 she was advised that her heart disease was not suitable for operation and was warned against having children. Attended hospital when three months' pregnant at the age of 23.

Examination. Slight central cyanosis. No clubbing of fingers. Pulse small. BP, 90/70. Jugular pulse showed prominent *a* wave. Pulsation in supra-sternal notch, and over the conus of RV and PA. Apex beat a little out. Palpable pulmonary valve closure. Second sound split in pulmonary area with loud pulmonary component. Short systolic murmur and thrill in PA.

Radiology. No generalized enlargement of the heart. Moderate enlargement of RA, and similarly of PA with slight pulmonary plethora. Aorta normal.

EC. S wave very deep in leads I and CR7 and equal to tall R in CR1 where S–T segment was depressed. T low only in lead III. P waves normal.

Course. Breathlessness increased during pregnancy, and was accompanied by hæmoptysis and œdema of the ankles. On admission to hospital the jugular venous pressure was raised to 5 cm. Considerable œdema of feet and legs. Hb, 113. WBC, 9·2. WR negative. Shock and unconsciousness developed during third stage of premature labour at 36 weeks. Became febrile, with rising pulse rate and deep central cyanosis, and died in coma on the fifth day of the puerperium.

Necropsy. Moderate congestion of viscera. No thrombosis in heart or in systemic veins.

Heart. Wt 305 g. Patent ductus arteriosus (1 cm. diameter); left PA and aorta contiguous at site of fistula. RV moderately dilated and greatly hypertrophied (1 cm. thick). LV normal (1·2 cm. thick). Fused and depressed commissure between small left and right coronary cusps of aortic valve of congenital origin.

Lungs. No infarction or thrombosis. Very severe atheroma extending down to segmental branches and confluent in main trunk.

Microscopy. Elastic arteries normal. Widespread occlusive changes in muscular arteries, and mainly in vessels with diameter below 0·5 mm. Such intimal proliferation frequently appeared as elastoid reaction. Focal or diffuse attenuation of media common in occluded or stenosed arteries. Some otherwise normal muscular arteries in state of contracture, with diameter as small as 0·06 mm. Majority of arterioles occluded by tissue similar to that in muscular arteries. Abundant collateral channels, many filled with intimal proliferation. Bronchial arteries and venules normal.

Case 9. E. G., married woman without children, aged 35, had been blue since the age of 14. She became breathless on effort at 29, when a diagnosis of congenital heart disease was made. She remained fairly well until she was 38, when she started having recurring hæmoptysis. Ten years later, dyspnœa became worse and œdema of the ankles developed. She was admitted to hospital following a large hæmoptysis.

Examination. Intense cyanosis, but no clubbing. Pulse regular and of good volume. BP, 140/80. Jugular venous pressure raised 3 cm. Apex beat just outside MCL. Right ventricular systolic lift. Palpable pulmonary valve closure. Sound in early systole in pulmonary area. Closely split second sound with loud pulmonary element. No murmurs heard. Hb, 130. RBC, 10·4.

Radiology. Only slight enlargement of heart, and RA not prominent. PA enlarged and bulging slightly from pulmonary bay; its primary branches conspicuous with calcium in their walls. Peripheral lung fields relatively clear. Aorta dilated and calcified.

EC. Sinus rhythm. S wave very deep in leads I and CR7 and absent in CR1 where R was tall. T wave low in I, and CR4 and inverted in II, III, CR1, and CR7. Tall P in II, CR1, CR4, and CR7.

Course. Re-admitted to hospital at age of 52 with heart failure. Graham Steell murmur audible. Several further hospital admissions for pulmonary infarction with fatal pulmonary embolism ultimately.

Necropsy. Congestion of viscera. No thrombosis in heart or in systemic veins.

Heart. FOP (valvular). Great hypertrophy without dilatation of RV (1·2 cm. thick). LV normal (1·5 cm. thick). Both atria normal. Calcification of pulmonary and tricuspid valve cusps. Aorta communicating directly with left PA by orifice of 1·5 by 0·8 cm. Calcified and ulcerated atheromatous plaque in aorta opposite ductus.

Lungs. Gross dilatation and calcification of pulmonary trunk and both branches. Confluent atheroma and calcification extending to branches of segmental arteries. Thrombus in right pulmonary artery. Several infarcts of vary-

ing ages in right lung. Bronchial arteries normal. Pulmonary arteriography showed left PA and segmental branches to be of normal calibre. Widespread occlusion of lobular arteries and loss of finest branches. Inter-pulmonary arterial anastomoses.

Microscopy. Severe atherosclerosis in elastic arteries whose media showed abundance of elastic laminæ suggesting arterial contracture. Scarcely a single muscular artery normal, the great majority being occluded, and many in course of disintegration. Occlusive process sometimes thrombotic. Great elastoid intimal proliferation. Media showed focal or diffuse hypoplasia and often aplasia. Collateral channels abundant both in vicinity of obliterated muscular arteries and beneath pleura. Most arterioles narrowed or occluded by intimal proliferation. Venules showed great endothelial thickening. Bronchial arteries prolific.

Case 10. J. M., a girl aged 15. A heart murmur had been discovered at the age of 4, cyanosis at 5, and scoliosis at 7 years. At 14, dyspnœa became evident and cyanosis had increased. She also developed aching in the jaw on effort.

Examination. Central cyanosis, but no clubbing. Pulse small. BP 110/95. Giant *a* wave in neck. Apex beat just outside MCL. Right ventricular pulsation in epigastrium. Pulmonary valve closure palpable. Sound in early systole and moderate systolic murmur in pulmonary area. Second sound closely split with loud pulmonary element. Severe kyphoscoliosis.

Radiology. Moderate enlargement of RA and RV. PA filling pulmonary bay. Right PA and segmental branches normal. Peripheral lung fields clear. Aorta small. Marked kyphoscoliosis.

EC. S wave very deep in leads I and CR7 and small in CR1 where R was tall. T wave inverted in leads II, III, and CR1. S–T depressed in CR7. P wave tall in lead II and tall and spiky in CR1.

Course. When admitted to hospital a pulmonary diastolic murmur was present. No œdema. Hb, 118. WBC, 9·6. Cardiac catheterization was attempted, but the patient's condition prevented completion of the test. She died suddenly a month after discharge from hospital and nine months after noticeable increase in breathlessness.

Necropsy. (Permission to examine heart and lungs only.)

Heart. Wt 280 g. Great hypertrophy of RV, which was as thick as LV (1·0 cm.). Patent ductus arteriosus, 1 cm. long and 1 cm. wide. No thrombosis.

Lungs. Occasional small plaques of atheroma in dilated PA trunk and main branches.

Microscopy. (Only two blocks were available for histological examination.) Elastic arteries normal. Large and medium-sized muscular arteries also normal apart from occasional thrombosis. Most conspicuous abnormality was contracture of small muscular arteries, some of which were no more than 0·04 mm. in diameter; a few showed slight intimal proliferation adjacent to areas of medial hypoplasia. Arterioles, venules, and bronchial arteries normal. Moderate emphysema.

Incidence

The diagnosis of pulmonary hypertension and patent ductus arteriosus was an infrequent event ten years ago, and even now it is not commonplace. Nevertheless, the dual lesion is not rare. Among 272 cases of patent ductus, Ellis *et al.* (1956) found 45 (16%) with a systolic pulmonary pressure of 60 mm. Hg or higher. Pedersen *et al.* (1956) found a systolic pressure of 80 mm. in 18 of 107 cases, and Lequime *et al.* (1956) reported considerable pulmonary hypertension in 15 per cent of their series. Campbell (1955) when collecting 160 cases of patent ductus arteriosus without pulmonary hypertension in the sense used here met with six with hypertension, and we encountered eight instances showing right ventricular preponderance in the electrocardiogram when assembling 100 uncomplicated cases.

Until recently most of the reported cases of patent ductus arteriosus with pulmonary hypertension have been adults. Thus, Anderson *et al.* (1956), reporting on 10 cases in children, reviewed 45 published cases with reversed or bi-directional flow, and only 5 of these were under 10, while 19 were over 30 years of age. Among 30 cases reported by Sones (1956), 18 were infants under 2 years, though his diagnosis of hypertension rested on manometric readings. Wood (1956) found an average of 16 years in his cases with hypertension to be almost identical with that in cases of uncomplicated patent ductus. The ages of our 4 cases at death were 15, 22, 24, and 55 years.

In Abbott's (1936) series of simple patency of ductus arteriosus the female incidence was about twice as common as the male, and Cosh (1957) found a female preponderance of 2·7 to 1 in his series. A slightly greater female preponderance is found when pulmonary hypertension is associated with the patent ductus. Thus, of the 45 cases reviewed by Anderson *et al.* (1956), 32 were female and 13 male. Four out of eight cases reported by Hultgren *et al.* (1953) were female, seven out of eight reported by Whitaker *et al.* (1955), and five out of six reported by Campbell (1955). Our four cases were female.

Clinical Features

Although cyanosis was present in each of our four cases, it was prominent in only one (Case 9) where there was thrombosis of the main branches of the pulmonary artery with noticeable calcification of their walls as far as the segmental branches. Clubbing of the fingers was never seen. Greater cyanosis in the lower than in the upper limbs has sometimes been described in patients in whom the shunt through the ductus has become reversed, but this differential cyanosis was not seen in our cases.

When pulmonary hypertension complicates patent ductus arteriosus the pulse is usually small, and a pulmonary diastolic shock is generally present. The typical continuous or Gibson murmur is absent. In three of our four cases a Graham Steell murmur was audible, and in two a systolic murmur. The absence of a Gibson murmur is significant. In early infancy when the systemic pressure is low and the pulmonary arterial pressure relatively high (Hamilton *et al.*, 1937; Barclay *et al.*, 1944), the blood flow through a patent ductus is small and takes place chiefly during systole. With the growth of the infant, the systemic blood pressure rises and the pulmonary arterial pressure falls, so that there is an appreciable blood flow through the ductus during both systole and diastole. The characteristic continuous murmur usually appears about the age of two or three years, though Taussig (1947) has observed a number of patients with a patent ductus and cardiac enlargement, who had not developed a typical murmur till the age of five or six years. Gilchrist (1945) pointed out that the characteristic murmur may disappear when congestive heart failure sets in, thus introducing a difficulty in diagnosis.

The absence of a Gibson murmur when pulmonary hypertension is present can be readily understood, for a rise in pressure within the pulmonary artery retards and eventually halts the entry of blood from the aorta. What does cause surprise, however, is the small number of patients so far reported in whom the characteristic ductus murmur had been noted before the diagnosis of pulmonary hypertension. Single instances of such disappearance of the Gibson murmur have been reported by Campbell and Hudson (1952), Burchell *et al.* (1953), Lukas *et al.* (1954), Harris (1955), and Whitaker *et al.* (1955). So far we have not met with an example of this, and we think there is a need to exercise caution in pronouncing on the presence of a Gibson murmur in this dual lesion since it may be closely simulated by the systolic and diastolic murmurs of pulmonary hypertension with pulmonary regurgitation. The rarity with which the disappearance of a Gibson murmur has been observed, before ligation of the ductus became common practice, suggests that pulmonary hypertension develops often at an early age in patients with a patent ductus.

The Electrocardiogram. In uncomplicated patent ductus arteriosus this is either normal or shows left ventricular preponderance. In the presence of pulmonary hypertension the tracing is dominated by the signs of right ventricular enlargement, though it may also show evidence of left ventricular enlargement (Fig. 6).

Radiology. The heart is only moderately enlarged as a rule, but the pulmonary trunk and its main branches may be considerably dilated and show exaggerated pulsation. The periphery of the lung fields tends to be abnormally translucent (Fig. 10 and 11).

Other Investigations. Reversal of the shunt may be diagnosed if the oxygen saturation of blood from the femoral artery is less than that from the brachial artery. Catheterization is of value in establishing the diagnosis of a patent ductus in the presence of pulmonary hypertension, for it is usually possible to pass the catheter through the ductus into the aorta. In this way not only may the anatomical diagnosis be confirmed, but the pressure gradient across the ductus and the pulmonary vascular resistance can be determined. Should it prove impossible to enter the ductus, this may be detected when there is still a left-to-right shunt, by finding a higher oxygen saturation in the pulmonary artery than in the right ventricle, although this is also found in other aorto-pulmonary communications.

Treatment. Surgical treatment of uncomplicated patent ductus arteriosus is an established procedure with a very low mortality (Gross, 1952; Neill and Mounsey, 1957). The success attendant

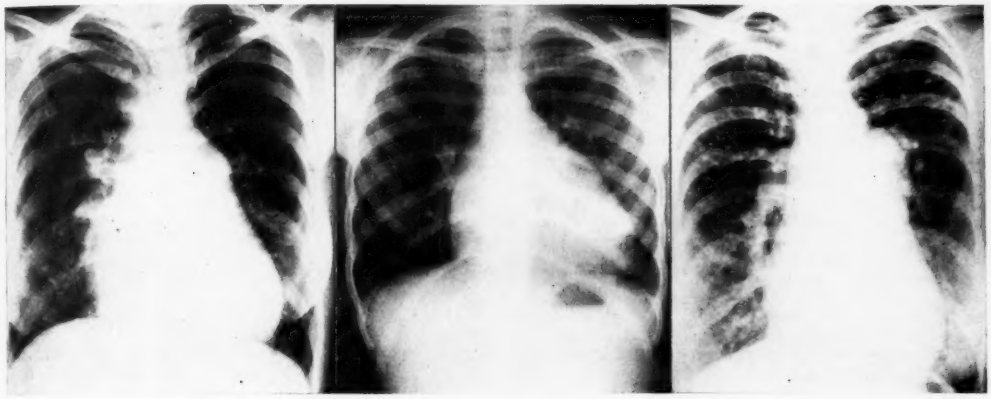


FIG. 10.—*Patent Ductus Arteriosus and Pulmonary Hypertension.* Considerable enlargement of RA, RV, and of PA and its primary branches. Periphery of lung fields clear. Case 7.

FIG. 11.—*Patent Ductus Arteriosus and Pulmonary Hypertension.* Enlargement of RA and of main PA, but not of its primary branches. *LV prominent* from displacement by enlarged RV. Periphery of lung fields clear. Case 10.

FIG. 12.—*Persistent Truncus Arteriosus and Pulmonary Hypertension.* Slight enlargement of RA and greater enlargement of RV. Left and right PA greatly dilated; their branches are visible as far as the periphery. Case 11.

on surgical treatment of a ductus associated with pulmonary hypertension inevitably depends on the ability of this procedure to reverse or retard the obstructive changes within the lesser pulmonary arteries and arterioles. Campbell (1955) stated that on the existing evidence it was unwise to assume that pulmonary hypertension was irreversible in any *child*, but that where the pressure had risen in infancy and the blood flow had been balanced or reversed, the surgical procedure was unlikely to reduce the high pressure because of the high arteriolar resistance and extensive structural changes in the pulmonary arterioles. Ellis *et al.* (1956) reviewed the progress following duct ligature of 30 cases in whom the pulmonary systolic pressure exceeded 60 mm. Hg. The mortality rate for the whole group was 18 per cent, and in those in whom a right-to-left shunt was present it was 56 per cent. They concluded that surgical closure of a ductus was hazardous when the shunt was predominantly from right to left or if, following temporary occlusion of the duct at the time of the operation, the pressure rose in the pulmonary artery and fell in the aorta. Anderson *et al.* (1956) who reviewed 45 reported cases of patent ductus with reversal of flow found that only four of them had a good result from surgical treatment and each of these probably had bi-directional shunts. Crafoord (1951) pointed out that the surgical risk was greater in cases with pulmonary hypertension even if the shunt was not reversed. Having regard to the nature and extent of the arterial changes that are present we believe that the ductus should not be ligated when pulmonary hypertension, as defined here, complicates patent ductus arteriosus.

PULMONARY HYPERTENSION IN DEFECTS OF THE AORTIC SEPTUM

Case Report

Case 11. D. B., a single woman, aged 35, was first seen at the age of 11 when she had slight cyanosis and a diastolic murmur down the left border of the sternum. She led a sheltered life, and complained of no symptoms until the age of 34, when she attended hospital complaining of palpitation, dyspnœa on effort, and a single small hæmoptysis.

Examination. Cyanosis, but no clubbing of fingers. Pulse irregular from frequent extrasystoles, but otherwise normal. BP, 120/75. Jugular venous pulse normal. Right ventricular systolic lift. Pulmonary valve closure shook the chest. Short and very coarse systolic murmur in pulmonary area, but without a thrill. Second sound split, with a very loud pulmonary element, and followed by Graham Steell murmur. Hb, 118; WBC, 10, 250.

Radiology. Slight enlargement of RA and greater of RV. Pulmonary trunk and left branch greatly dilated, but not abnormally pulsatile. Right PA prominent. Aorta somewhat dilated and more pulsatile than usual. Lung fields clear.

EC. Sinus rhythm; no extrasystoles recorded. S wave small in I and absent in leads CR1 and CR7. Tall R in same three leads. T inverted in CR1, CR2, and CR3 and very low in lead I. P wave moderately tall in CR1.

Cardiac Catheterization. PA mean pressure 83 mm. Hg. Arterialization of blood in PA confirmed the presence of a communication between aorta and PA.

Course. She was considered to be a case of pulmonary hypertension in patent ductus arteriosus although the diagnosis of an aorto-pulmonary fistula was also entertained. A gross aortic septal defect was discovered at operation. An attempt was made to repair it, but the patient died on the operating table.

Necropsy. Customary changes of heart failure in viscera. No thrombosis in heart or in systemic veins.

Heart. Wt 468 g. Great hypertrophy of RV (1·5 cm. thick) and slight of LV (1·5 cm. thick). Dilatation of RA and LA. Valves normal. No cardiac septal defects. Coronary arteries arising normally from aortic sinuses.

Lungs. Pulmonary trunk and aorta were joined to form a single grossly dilated vessel immediately on leaving heart and as far as bifurcation of PA. Wall of vascular swelling very thin. Both PAs greatly dilated. Right PA leaving conjoined aortic and pulmonary trunk posteriorly, and left PA turning immediately to left. Pulmonary arteriography showed right pulmonary artery and its segmental branches to be moderately dilated. Lobular arteries ended blindly with absence of their finest branches, and the presence of a dense network of tortuous anastomotic channels. Numerous areas of opaque material indicating infarcts.

Microscopy. Flecks of atheroma in elastic arteries. Muscular arteries, larger than 0·4 mm. in diameter, normal, but great majority of smaller ones narrowed or occluded by intimal elastoid proliferation. Hypoplasia and often aplasia of media in many of these vessels. Similar intimal elastoid proliferation occluding many arterioles while others were in process of disintegration. Collateral channels abundant near obstructed muscular arteries, and many showed either thrombosis or intimal proliferation. Venules showed moderate endothelial thickening. Bronchial arteries prolific. Numerous pulmonary infarcts.

Incidence

Defects of the aortic septum appear in three forms, all of which are uncommon. The first is the serious defect, of which our case is an example, where the aorta and pulmonary trunk form a common arterial trunk (persistent truncus). In the second variety the fistula connects the aorta with the right ventricle or sometimes with the right atrium. The third is the rare condition where the right aortic sinus opens into the pulmonary trunk: the communication in this instance is usually small and measures about 1 cm. in diameter (Dadds and Hoyle, 1949).

There were 21 cases of common arterial trunk in Abbott's series; in 18 where sex was noted 11 were male and 7 female. One survived to 25 years of age, but the mean age at death was only 4 years.

It is not possible to tell the incidence of pulmonary hypertension in the reported cases of common arterial trunk because the electrocardiogram, if recorded, has been an inadequate tracing for a firm opinion to be given on the presence of right heart preponderance, and the pulmonary arterial pressure has seldom been available. In Abbott's series two-thirds of the cases had right ventricular hypertrophy, and in the patient reported by Bain and Parkinson (1943), which closely resembled ours, the wall of the right ventricle was 1·0 cm. thick.

With an experience limited to one case of a persistent truncus and pulmonary hypertension we are disinclined to speak of special clinical features that help in the diagnosis of the conjoined lesion, except that the electrocardiogram may show evidence of biventricular enlargement, and cardioscopy may show much pulsation and prominence in the customary position of the ascending aorta as well as in the pulmonary artery (Fig. 12).

Surgical closure of an aorto-pulmonary fistula is possible, although unwise in the presence of pulmonary hypertension, but such treatment is not yet possible in the case of a persistent truncus.

Pathology

The findings at necropsy have been given in detail under the separate case reports. Here we describe the pathological features relating to the added pulmonary hypertension.

Apart from the significant congenital fistulae, there were other congenital anomalies in 8 of our 11 cases. These included a strawberry nævus of the cheek in Case 3, a hypoplastic aorta in Case 5, a small atrial septal defect in Case 6, a small valvular patency of the foramen ovale in Cases 4 and 9, fused aortic cusps in Case 8, fenestration of the aortic cusps in Case 4, marked kyphoscoliosis in

FIG. 13.—*Pulmonary Arteriogram.* (A) is from a patient with uncomplicated atrial septal defect. The defect was so great that the atria formed virtually a single chamber. (B) is from Case 1 with plumonary hypertension complicating atrial septal defect. The segmental arteries are enormously dilated. Many of the lobular arteries end abruptly, and the finest branches are lost throughout most of the lung, but in some areas the peripheral pattern is normal.

Case 10, and Madelung's deformity, with absence of the left uterine cornu and Fallopian tube and displacement of the left kidney to the right side in Case 7.

The Heart. This was always heavier than normal. The right ventricle was invariably hypertrophied and was usually moderately dilated. Its thickness varied between 7 and 15 mm. with a mean of 11 mm. The left ventricle was hypertrophied only in the cases with ventricular septal defect. The right atrium was only slightly dilated and hypertrophied, except in the cases with atrial septal defect and in one case with patent ductus arteriosus where both dilatation and hypertrophy were greater. Intracardiac thrombosis was present only once.

The Lungs. The lung parenchyma was normal except for areas of infarction which appeared in 5 of the 11 cases. The pulmonary trunk was always dilated, and so as a rule were the main segmental branches; this change was particularly noticeable in patients with atrial septal defect. Mod-

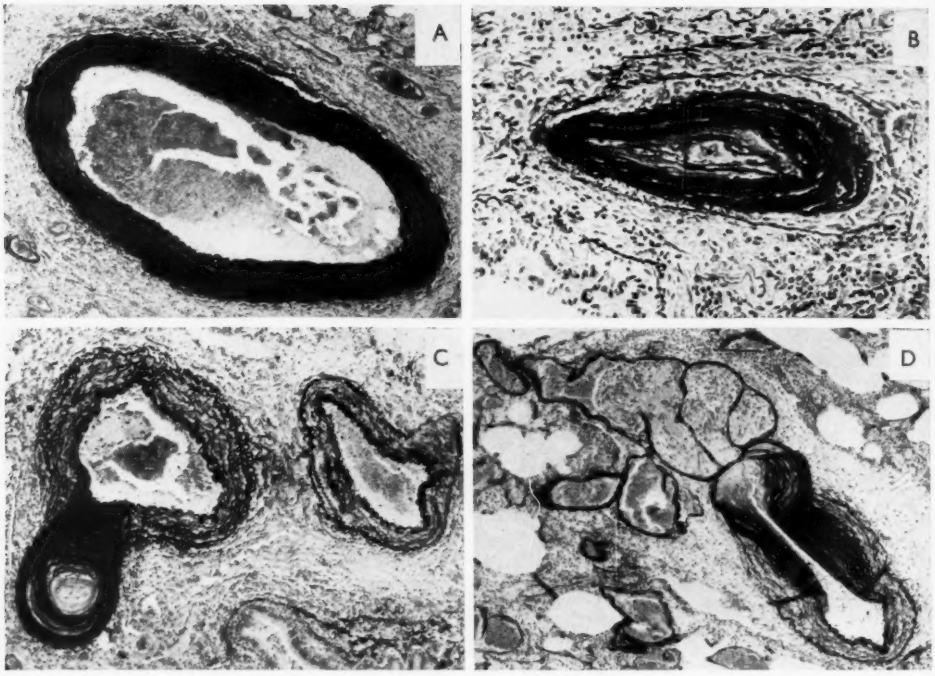


FIG. 14.—*Patent Ductus Arteriosus and Pulmonary Hypertension.* (A) Elastic reduplication in media of small elastic artery (1·1 mm. diam.) probably indicating arterial contracture. ×20. (B) Elastoid intimal proliferation which almost occludes muscular artery (0·14 mm. diam.) whose media is greatly thinned on its inferior aspect. ×152. (C) Elastoid proliferation within branch or collateral channel arising from contracted elastic artery (0·56 mm. diam.). ×63. (D) Collateral channels filled for most part by organizing thrombus. ×41. Case 8.

erate atherosclerosis was usually present in these vessels, and in one case of patent ductus arteriosus there was severe intimal calcification extending from the pulmonary trunk as far as the segmental arteries. In two cases the right or the left pulmonary artery was occluded by thrombus, and in four others thrombus had either partly or completely closed a segmental artery. The bronchial arteries in their extra-pulmonary course were normal.

Pulmonary Arteriography. Although we hold that this investigation should have pride of place in the post-mortem examination of any case of pulmonary hypertension, the opportunity was only afforded us in three of our cases, and in one control case with a large atrial septal defect without pulmonary hypertension. In the control case the pulmonary trunk and its branches were moderately dilated, and the pulmonary vascular pattern was normal (Fig. 13A). In the cases of pulmonary hypertension the appearances were similar to those found in pulmonary hypertension associated with mitral stenosis or occurring alone, and indicated obstruction within the lesser pulmonary arteries and arterioles. The obstructed arteries were approximately 0·5 to 2·0 mm. diameter in one case, 0·2 mm. in the second, and 0·4 mm. in the third case. Such vessels were seen to end blindly (Fig. 13B) and in many places the normal arteriolar pattern was replaced by tortuous collateral channels. Infarcted areas were present in the control case and in two of the cases with pulmonary hypertension.

Histological Findings. The pulmonary arteries in uncomplicated atrial septal defect, ventricular septal defect, and patent ductus arteriosus show only patchy intimal thickening similar to that in control subjects (Welch and Kinney, 1948; Edwards, 1955). The changes found on microscopical examination of the lungs in our 11 cases with pulmonary hypertension were uniform, nor did they differ in any important respect from those found in solitary pulmonary hypertension (Evans *et al.*, 1957).

In 9 of the 11 cases there was widespread obstruction in the muscular (0·1 to 1·0 mm. diameter, and small elastic arteries slightly exceeding 1·0 mm. diameter. In the remaining two the changes were less noticeable although in both of these only a limited number of sections were available. In four cases the main obstruction was in the small elastic and the large muscular arteries; in four the brunt fell on the medium-sized muscular arteries, and in one on the small muscular arteries. In the elastic arteries the tissue that blocked the vessels often had the appearance of organizing thrombus. In the muscular arteries the tissue was usually fibrotic and seemed reactive and reparative rather than passive, and we have described this change as *intimal proliferation.* In seven of our cases this newer tissue contained an abundance of elastic fibres and we have referred to this as *elastoid intimal proliferation* (Fig. 14). Such reaction was commoner in pulmonary hypertension associated with congenital shunts than in that associated with mitral stenosis or occurring alone.

The intimal proliferation usually overlay segments of *medial hypoplasia*, while sometimes this weakness of the arterial wall amounted to *aplasia*, the vessel showing only a single elastic layer, and thus resembling an arteriole except for its larger size (Fig. 15, 16, 17, and 18).

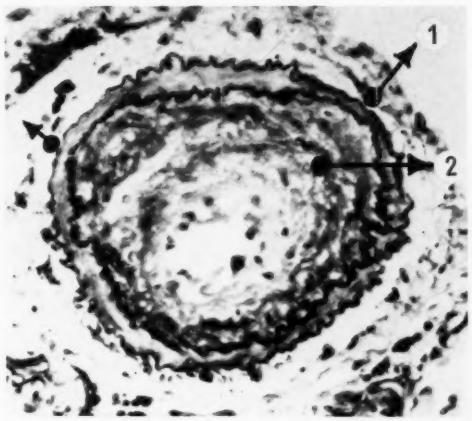


FIG. 15.—*Atrial Septal Defect and Pulmonary Hypertension.* Hypoplasia (1) of media of muscular artery (0·16 mm. diam.). Intimal proliferation (2) almost occluding the lumen. ×300. Case 1.

Collateral channels, similar to those described by Brewer (1955), were abundant in seven cases in which the main obstruction was in the medium-sized or larger muscular arteries; they were situated near the site of obstruction. When empty, such channels appeared as spaces surrounded by a thin layer of endothelium supported by an elastic membrane. Frequently, however, they were filled with organizing tissue which sometimes showed canalization (Fig. 14D, 16C, and 16D).

Only a limited number of sections were available for histological examination in the two cases in which intimal proliferation was inconspicuous. The most striking abnormality in these was the presence of a distinct muscular coat in vessels of arteriolar size (less than 0·1 mm. diameter), and

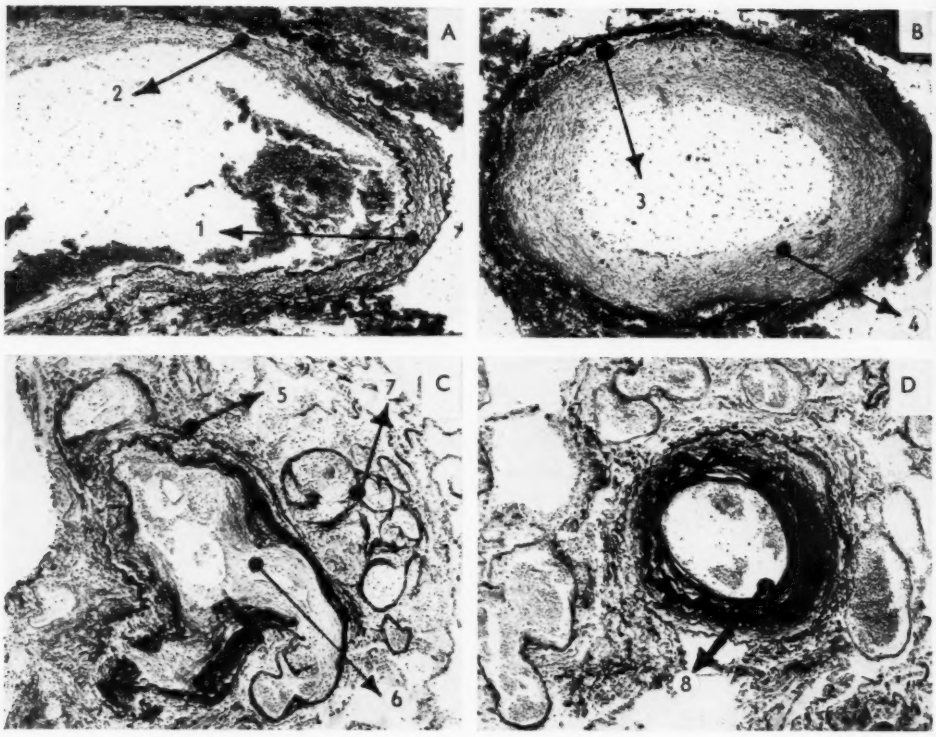


FIG. 16.—*Ventricular Septal Defect and Pulmonary Hypertension.* (A) Muscular artery (0·86 mm. wide) showing normal media at (1), and aplasia with adjacent intimal proliferation at (2). (B) Aplasia (3) of entire circumference of muscular artery (0·9 mm. diam.) with intimal proliferation (4) which greatly narrows lumen. (C) Collateral channels (6 and 7), the majority of which are filled with organizing thrombus, arising from muscular artery (5) greatly narrowed by intimal proliferation. ×47. (D) Elastoid intimal proliferation (8) within muscular artery (0·65 mm. diam.) whose media shows hypoplasia. ×47. Case 6.

apparent medial hypertrophy in the larger arteries (Fig. 19). These changes were also present in 6 of the 9 cases with prominent intimal proliferation. Similar changes were found in our cases of mitral stenosis with pulmonary hypertension (Evans and Short, 1957). Arteriography has shown that these vessels are relatively indistensible and we have described this diffuse intractable narrowing as *arterial contracture*.

PATHOGENESIS

Any theory that purports to explain the development of pulmonary hypertension in the presence of cardiac or aorto-pulmonary shunts must account for the severe and widespread arterial obstruction, which is invariably found at necropsy.

These arterial lesions are not merely terminal. This is evident both from the histological appearances, and from the fact that similar lesions are found in lung sections taken at operation (Heath and Whitaker, 1955). This explains why the pressure in the pulmonary artery does not fall when the shunt is arrested, as in the case of ligation of the ductus (Shephard, 1954).

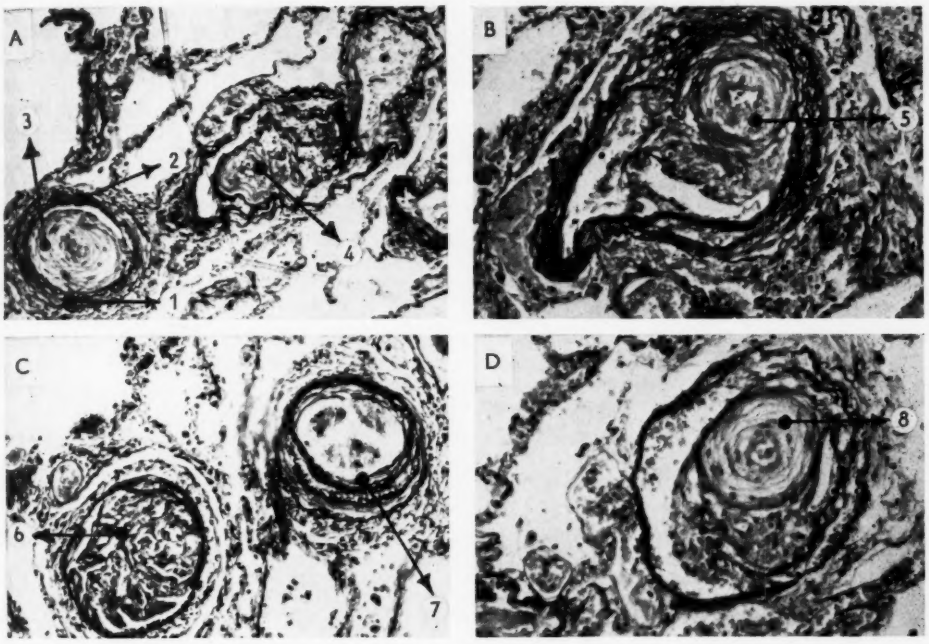


FIG. 17.—*Atrial Septal Defect and Pulmonary Hypertension.* (A) Hypoplasia (1) (2) of media of muscular artery (0·19 mm. diam.) containing organizing thrombus (3). Similar thrombus (4) in a collateral vessel. ×95. (B) Intimal proliferation and thrombosis (5) in muscular artery (0·23 mm. diam.) showing medial hypoplasia adjacent to it. (C) Thrombus (6) in a collateral vessel and elastoid intimal proliferation (7) in a muscular artery (0·17 mm. diam.) part of whose wall shows aplasia. ×125. (D) Re-canalization (8) of muscular artery (0·20 mm. diam.) which shows aplasia and hypoplasia of its media. ×175. Case 2.

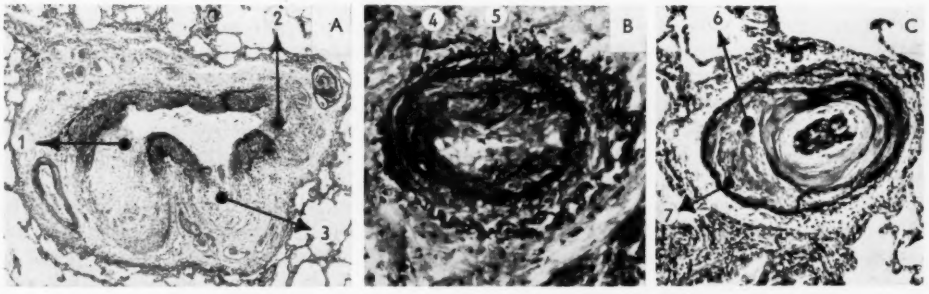


FIG. 18.—*Patent Ductus Arteriosus and Pulmonary Hypertension.* (A) Breaches (1, 2, and 3) in the media of a muscular artery (0·45 mm. wide) filled with organizing thrombus. ×26. (B) Hypoplasia of media (4) of muscular artery (0·25 mm. diam.) with intimal proliferation (5) which almost occludes its lumen. ×125. (C) Similar proliferation (6) and thrombosis within muscular artery (0·30 mm. diam.) which shows segmental medial aplasia (7). ×80. Case 7.

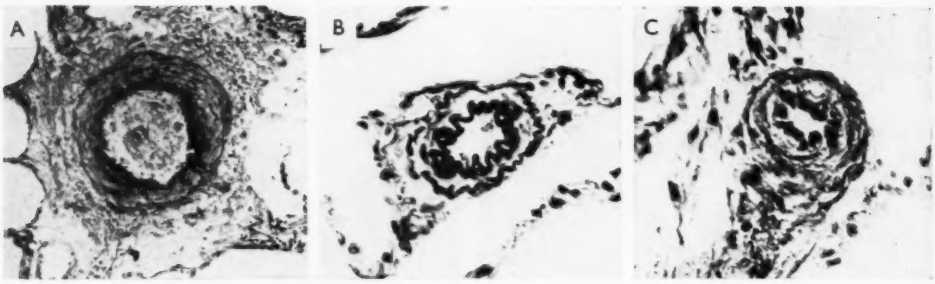


FIG. 19.—*Ventricular Septal Defect and Pulmonary Hypertension.* (A) Apparent hypertrophy of muscular artery (0·30 mm. diam.), probably indicating arterial contracture. ×80. (B) Contracture of muscular artery (40μ diam.) with deep crenation of the internal elastic lamina. ×400. (C) Intimal proliferation, with pallisading effect within arteriole (40μ diam.) which is the same size as muscular artery in B. ×400. Case 5.

Pulmonary embolism and thrombosis are important aggravating factors once pulmonary hypertension has developed (Dexter, 1956), but there is no evidence that they initiate the hypertension. Pulmonary arteritis has occasionally been described in cases of pulmonary hypertension (Old and Russell, 1950), but as a rule there is no histological evidence of inflammation or scarring.

It is widely held that the development of pulmonary hypertension is related to the magnitude of the left-to-right shunt (Swan *et al.*, 1954). It has been said that hypertension is commoner in the presence of a large ventricular septal defect or ductus than a small one. Nevertheless, by no means all patients with a large ductus develop hypertension. Campbell (1955) observed that some of the patients with large shunts reached a good age and developed left ventricular failure without evidence of pulmonary hypertension. We have not found any correlation between the size of the shunt and the presence or absence of pulmonary hypertension. The diameters of the duct in our four cases for instance were 0·9, 1·0, 1·5, and 1·0 cm. respectively. In 47 cases of patent ductus without pulmonary hypertension treated surgically at the London Hospital in whom a measure of the ductus was taken, 25 were classified as small (0·25 to 0·75 cm. diam.), 10 as medium (0·75 to 1·0 cm. diam.) and 12 as large (over 1·0 cm. diam.) (Mounsey, 1957). Furthermore, pulmonary hypertension may be found in association with a small ductus (Limon-Lason *et al.*, 1950). We do not, therefore, subscribe to the view that an increase in the pulmonary blood flow is the cause of pulmonary hypertension, although it can hasten its progression in the presence of another ætiological factor.

Such considerations suggest that there is a congenital predisposition to pulmonary hypertension in certain patients. Edwards (1950) has pointed to the similarity between the apparently hypertrophied arteries of the patient with hypertension and the thick-walled arteries of the fœtus, and has postulated that in patients who will develop hypertension, the fœtal state persists into childhood. Edwards (1957) believes that the obliterative lesions develop later as a specific effect of severe chronic hypertension. The main objection to Edwards' theory is that apparently similar thick-walled arteries are found in pulmonary hypertension associated with mitral stenosis, and it is very difficult to believe that the arterial abnormality here is an independent condition present from birth. Furthermore, there is some evidence that in cases of congenital heart disease destined to develop hypertension the normal evolution of the pulmonary arteries takes place in the early months of post-natal life. Thus, Dammann and Ferencz (1956) have shown that the pulmonary vascular resistance in cases with a large ventricular septal defect tends to fall toward normal in the early post-natal months. Brotmacher and Campbell (1958) also imply that the resistance is not as a rule high in infancy, but rises gradually with the passage of years.

The evidence obtained by correlating post-mortem arteriography with histology indicates that the apparent medial hypertrophy is an expression of persistent, diffuse, organic constriction, which

we have termed arterial contracture. The manner in which arterial contracture develops is not known. Bayliss (1902) showed that the muscular coat of arteries, like smooth muscle in other situations, reacts to a stretching force by contraction. A moderate rise in pressure from any cause, e.g. increased blood flow, induces in susceptible subjects abnormal vasoconstriction (Wood, 1952), and this, if it persists, leads ultimately to persistent shortening of the muscular fibres and elastic laminæ (Short, 1957). If it is assumed that the inherent responsiveness of the arteries to a raised pressure is not universal, but varies from one subject to another, it may explain the development of pulmonary hypertension. Occlusive changes would then be regarded as a late development leading to reversal of the shunt, as Dammann and Ferencz (1956) and Edwards (1957) have suggested.

That inherent weakness of the media of the lesser pulmonary arteries is responsible for the complication of pulmonary hypertension in congenital heart disease was a view first advanced by Evans (1951) who was so impressed with its association with congenital fistulæ, that he referred to it as congenital pulmonary hypertension. That such medial deficiencies played an ætiological role in pulmonary hypertension was first postulated by Gilmour and Evans (1946) in a case of so-called primary pulmonary hypertension. They believed that in this condition the intimal proliferation occurred over some of those deficiencies, which numbered several thousands, during attacks of mild and transient hypertension as might have been produced by coughing, and that subsequently the resulting arterial stenosis or occlusion led to persistent hypertension.

In the case of cardiac and aorto-pulmonary shunts the pressure in the pulmonary artery rises. If this takes place in the presence of congenital hypoplasia or aplasia in the media of the lesser pulmonary arteries, it is postulated that intimal proliferation results, leading to progressive obstruction of the arteries and severe persistent hypertension.

Whatever the nature of the congenital anomaly responsible for the development of pulmonary hypertension there are certain circumstances that inevitably aggravate the condition. Pulmonary embolism and thrombosis have already been mentioned. Whittaker and Winton (1933) showed that an increase in corpuscular concentration above the normal leads to a considerable rise in viscosity and therefore to an increase in the vascular resistance. Again, the system of collateral channels which develops when large arteries are obstructed must be an inefficient substitute for the normal pathway. Moreover, their width and tortuosity make them very liable to thrombosis, and this event may actually precipitate the death of some of the patients.

Summary and Conclusions

The pulmonary vasculature was specially examined at necropsy in 11 patients in whom a congenital intracardiac or aorto-pulmonary communciation was complicated by pulmonary hypertension. The congenital anomaly was an atrial septal defect in three cases, a ventricular septal defect in three, a patent ductus arteriosus in four, and a common aorto-pulmonary trunk in one case.

We have adhered to the definition of pulmonary hypertension as a state of persistent elevation of the pulmonary arterial pressure sufficient to cause enlargement and ultimately failure of the right ventricle, and with characteristic clinical, electrocardiographic, and radiological signs. The diagnosis in our patients was made without recourse to pulmonary arterial catheterization.

The changes in the pulmonary arteries among our 11 cases were uniform, and did not depend on the position of the congenital communication. They differed in no important respect from those found in solitary pulmonary hypertension or in hypertension associated with mitral stenosis.

The pulmonary arteriogram showed great restriction of the peripheral arterial bed throughout the lung. Histological examination demonstrated widespread obstruction of arteries less than 2 mm. in diameter by intimal proliferation in which thrombosis with subsequent organization played a part. The muscular arteries were particularly affected, and in them the intimal proliferation, usually in the form of an elastoid reaction, was associated with hypoplasia or even aplasia of the media. Near occluded arteries there were often large collateral channels, which were sometimes filled with

organizing thrombus. Diffuse arterial contracture was frequently seen in the muscular arteries, which were often as small as 0·04 mm. in diameter.

This investigation has established that vascular obstruction accounts for persistent pulmonary hypertension in congenital heart disease. In the circumstance, closure of the septal defect or ductus arteriosus cannot be curative.

The presence of such pulmonary vascular disease is not directly related either to the age of the patient or to the size of the congenital communication. We conclude that there resides in the pulmonary arteries an inherent predisposition to the development of arterial obstruction leading to pulmonary hypertension.

Although pulmonary hypertension has not been an uncommon clinical finding among our patients with congenital heart disease, the opportunity to examine 11 cases at necropsy could not have been given us except through the help of many colleagues. Professor Dorothy Russell has made available the material obtained at necropsy in eight of the cases. Cases 3, 5, 6, and 8 were one time under the care of Dr. Wallace Brigden, while Dr. Robert Benson supervised Case 6 during the last phase of his illness and supplied us with material obtained at necropsy. It was through the kindness of Dr. Frederic Jackson, Mr. George Mason, and Dr. B. E. Tomlinson that we were able to include Case 11 in the series. Dr. R. Hudson helped us with Case 2 which was under the care of Dr. Graham Hayward. Necropsy material was made available to us by Dr. T. V. Cooper in Case 4, and by Dr. L. W. B. Dobbin in Case 10. To these several colleagues we wish to express our great indebtedness for their help.

REFERENCES

Abbott, M. E. (1936). *Atlas of Congenital Heart Disease*. New York.
Anderson, R. C., Adams, P., and Varco, R. L. (1956). *Pediatrics*, **18**, 410.
Bain, C. W. C., and Parkinson, J. (1943). *Brit. Heart J.*, **5**, 97.
Barber, J. M., Magidson, O., and Wood, P. (1950). *Brit. Heart J.*, **12**, 277.
Barclay, A. E., Franklin, K. J., and Prichard, M. L. (1944). *The Foetal Circulation and Cardiovascular System and Changes they Undergo at Birth*. Oxford.
Bayliss, W. M. (1902). *J. Physiol.*, **28**, 220.
Bedford, D. E. (1957). Personal communication.
——, Sellors, T. H., Somerville, W., Belcher, J. R., and Besterman, E. M. M. (1957). *Lancet*, **1**, 1255.
Brewer, D. B. (1955). *J. Path. Bact.*, **70**, 299.
Brotmacher, L., and Campbell, M. (1958). *Brit. Heart J.*, **20**, 97.
Brown, J. W., Heath, D., and Whitaker, W. (1955). *Brit. Heart J.*, **17**, 273.
Burchell, H. B., Swan, H. J. C., and Wood, E. H. (1953). *Circulation*, **8**, 681.
Campbell, M. (1951). *Brit. Heart J.*, **13**, 438.
—— (1955). *Brit. Heart J.*, **17**, 511.
——, and Hudson, R. (1951). *Guy's Hosp. Rep.*, **100**, 26.
——, —— (1952). *Guy's Hosp. Rep.*, **101**, 32.
——, Neill, C., and Suzman, S. (1957). *Brit. med. J.*, **1**, 1375.
Cosh, J. A. (1957). *Brit. Heart J.*, **19**, 13.
Crafoord, C. (1951). *Brit. med. J.*, **1**, 946.
Dadds, J. H., and Hoyle, C. (1949). *Brit. Heart J.*, **11**, 390.
Dammann, J. F., and Ferencz, C. (1956). *Amer. Heart J.*, **52**, 210.
Dexter, L. (1956) *Brit. Heart J.*, **18**, 209.
DuShane, J. W., Kirklin, J. W., Patrick, R. T., Donald, D. E., Terry, H. R., Burchell, H. B., and Wood, E. H. (1956). *J. Amer. med. Ass.*, **160**, 950.
Edwards, J. E. (1950). *Proc. Inst. Med., Chicago*, **18**, 134.
—— (1955). In *Cardiovascular Surgery*. W. B. Saunders.
—— (1957). *Circulation*, **15**, 164.
Ellis, F. H., Kirklin, J. W., Callahan, J. A., and Wood, E. H. (1956). *J. thorac. Surg.*, **31**, 268.
Espino-Vela, J., and Mata, L. A. (1956). *Amer. Heart J.*, **51**, 284.
Evans, W. (1951). *Proc. Roy. Soc. Med.*, **44**, 600.
——, and Short, D. S. (1957). *Brit. Heart J.*, **19**, 457.
——, ——, and Bedford, D. E. (1957). *Brit. Heart J.*, **19**, 93.
Gilchrist, A. R. (1945). *Brit. Heart J.*, **7**, 1.
Gilmour, J. R., and Evans, W. (1946). *J. Path. Bact.*, **58**, 687,
Gross, R. E. (1952). *Amer. J. Med.*, **12**, 472.
Hamilton, W. F., Woodbury, R. A., and Woods, E. B. (1937). *Amer. J. Physiol.*, **119**, 206.
Harris, P. (1955). *Brit. Heart J.*, **17**, 85.
Heath, D., and Whitaker, W. (1955). *J. Path. Bact.*, **70**, 285.
Hultgren, H., Selzer, A., Purdy, A., Holman, E., and Gerbode, F. (1953). *Circulation*, **8**, 15.
Lequime, J., Denolin, H., and Hanson, J. (1956). *2nd European Congress of Cardiology*, Stockholm.
Limon-Lason, R., Bouchard, F., Rubio-Alvarez, V., Cahen, P., and Novelo, S. (1950). *Arch. Inst. Cardiol. Mexico*, **20**, 147.

Lukas, D. S., Araujo, J., and Steinberg, I. (1954). *Amer. J. Med.*, **17**, 298.
Mounsey, J. P. D. (1957). Personal communication.
Neill, C., and Mounsey, J. P. D. (1958). *Brit. Heart J.*, **20**, 61.
Old, J. W., and Russell, W. O. (1950). *Amer. J. Path.*, **26**, 789.
Pedersen, A., Davidsen, H. G., Fabricus, J., and Hansen, A. T. (1956). *2nd European Congress of Cardiology*, Stockholm.
Selzer, A., and Laqueur, G. L. (1951). *Arch. intern. Med.*, **87**, 218.
Shephard, R. J. (1954). *Brit. Heart J.*, **16**, 361.
Short, D. S. (1957). *Lancet*, **2**, 12.
Sones, F. M. (1956). *J. thorac. Surg.*, **31**, 283.
Swan, H. J. C., Zapata-Diaz, J., Burchell, H. B., and Wood, E. H. (1954). *Amer. J. Med.*, **16**, 12.
Taimont, F., Carouso, G., Mège, A., and Lenègre, J. (1952). *Arch. Mal Cœur*, **45**, 927.
Taussig, H. B. (1947). *Congenital Malformations of the Heart*. Commonwealth Fund, New York.
Wagner, J., and Graham, G. R. (1957). *Brit. Heart J.*, **19**, 318.
Walker, W. J., Mattingly, T. W., Pollock, B. E., Carmichael, D. B., Inmon, T. W., and Forrester, R. H. (1956). *Amer. Heart J.*, **52**, 547.
Welch, K. J., and Kinney, T. D. (1948). *Amer. J. Path.*, **24**, 729.
Whitaker, W., Heath, D., and Brown, J. W. (1955). *Brit. Heart J.*, **17**, 121
Whittaker, S. R. F., and Winton, F. R. (1933). *J. Physiol.*, **78**, 339.
Wood, P. (1952). *Brit. med. Bull.*, **8**, 348.
—— (1956). *Diseases of the Heart and Circulation*. 2nd Edition. Eyre and Spottiswoode, London.
——, Wilson, P. O., and Magidson, O. (1954). *Brit. Heart J.*, **16**, 387.

FŒTAL PAROXYSMAL AURICULAR TACHYCARDIA

BY

C. W. KESSON

From the Children's Department, St. George's Hospital

Received January 7, 1958

Although paroxysmal auricular tachycardia is most common in adults between the ages of 20 and 40 years, many examples of its occurrence in children have been described following Buckland's (1892) account of the condition in an eleven-year-old girl. During the past 25 years the arrhythmia has been recognized in antenatal life and the present paper reports two further examples affecting the fœtus.

Case Reports

Case 1. P.H. was the second child of healthy parents. The mother's first pregnancy in 1944 was uneventful and at term she was delivered of a normal, female child. Three years later in 1947 the mother had a miscarriage at two months. Her third pregnancy in 1949 was normal until two weeks before the expected date of delivery when there was a sudden increase in the size of her abdomen, due to the development of hydramnios, which necessitated her admission to hospital. A plain X-ray of the mother's abdomen showed the baby to be in full extension, a position considered to be the result of gross distension of the fœtal abdomen. The fœtal heart rate was recorded as varying between 130 and 140 beats a minute, the rhythm being regular. Two days after the mother was admitted to hospital her membranes were ruptured artificially, labour commenced within an hour and 9½ hours later she was delivered of a live, female child.

At birth the baby was very ill with severe dyspnœa and cyanosis. There was extensive œdema affecting the skin and subcutaneous tissues of the limbs, face, chest, and abdomen. The abdomen was distended by fluid in the peritoneal cavity. The heart size and cardiac sounds were normal The heart rate was above 200 beats a minute and the rhythm appeared regular although electrocardiography (Fig. 1) revealed the rate to be 228 beats a minute with a slight irregularity of the rhythm. The tracing was consistent with a 1:1 auricular tachycardia. A chest X-ray showed the heart to be normal in size, shape, and position; the lung fields were clear.

The child was nursed in an oxygen tent and no fluids were administered during the first 48 hours of life. Ten hours after birth quinidine sulphate was administered orally in the dose of 1/6 grain, four-hourly, but as there was no slowing of the heart rate and her condition deteriorated, the quinidine was abandoned after 24 hours and digoxin substituted in a dosage of 0·125 mg. intramuscularly at two-hourly intervals for three doses. An immediate response followed (Fig. 2) with the heart rate falling to 120 beats a minute and there was an associated improvement in the baby's condition. An electrocardiogram taken at this period confirmed that the cardiac rate and rhythm were normal. Following a large diuresis the œdema subsided rapidly and by the ninth day the weight had dropped from the birth weight of 9 lb. 1 oz. to 6 lb. 5¾ oz. Breast feeding was satisfactorily established and the baby was discharged home on the twelfth day of life weighing 6 lb. 8¾ oz.

At the age of six weeks, a routine visit was made to Out-Patients where it was found that her general progress had been satisfactory. The heart rate, however, was again over 200 beats a minute, though there was no evidence of cardiac failure. She was admitted to hospital where an electrocardiogram confirmed the recurrence of the auricular tachycardia. Digoxin was again administered in the dosage of 0·125 mg. two-hourly for three doses. Normal rhythm was re-established at once and there were no further attacks of cardiac arrhythmia during the following eight years of routine observation.

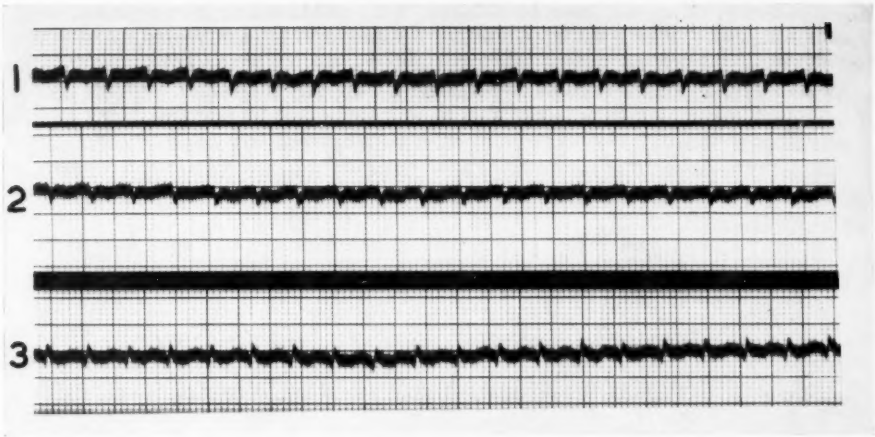


FIG. 1.—Case 1. Electrocardiogram taken on the first day of life, demonstrating the supraventricular tachycardia. Standard leads.

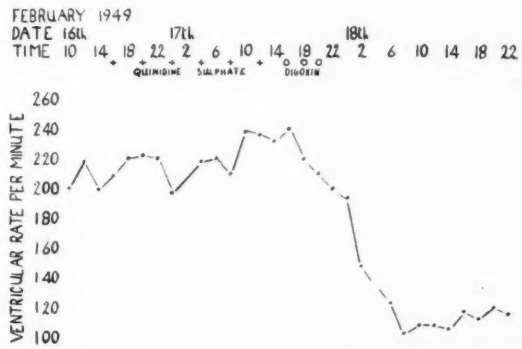


FIG. 2.—Case 1. Graph, showing the effect of quinidine and digoxin on the heart rate.

Case 2. C.K. was the first child of healthy parents. The mother's pregnancy was normal until a month before the expected date of delivery when she developed abdominal pain which was thought to be the onset of labour and she was admitted to hospital. At this time it was observed that the fœtal heart rate although regular was very rapid, over 200 beats a minute. After 24 hours rest in bed the mother's abdominal pains ceased and the fœtal heart rate slowed to 140 beats a minute (Fig. 3). Three days later, however, the fœtal tachycardia returned but attempts to obtain an electrocardiogram were unsuccessful. The mother was detained in hospital, although symptom-free, for a month when she went into labour spontaneously and was delivered normally of a male child weighing 8 lb. 14 oz.

On examination the child was healthy, and the heart beats regular at a rate of 140 a minute. The heart size and sounds were normal as, too, was the electrocardiogram. A chest X-ray revealed no abnormality. Breast feeding was readily established and the infant discharged home on the twelfth day weighing 9 lb. The child has attended Out-Patients at intervals since that time and was last seen when 4½ years of age. There is no evidence of any congenital abnormality of the heart.

The evidence suggests that both these patients developed auricular tachycardia during antenatal life. In Case 1, although no abnormality of the cardiac rate was detected before birth, the baby was born in congestive failure with auricular tachycardia. The recognition of the fœtal abdominal distension prior to the onset of labour strengthens the belief that cardiac embarrassment must have been of at least some days duration.

In the second baby, although it was not possible to obtain electrocardiographic evidence that the fœtus had auricular tachycardia, there is no other satisfactory explanation for a prolonged tachycardia of such degree terminating in the delivery of a normal healthy baby.

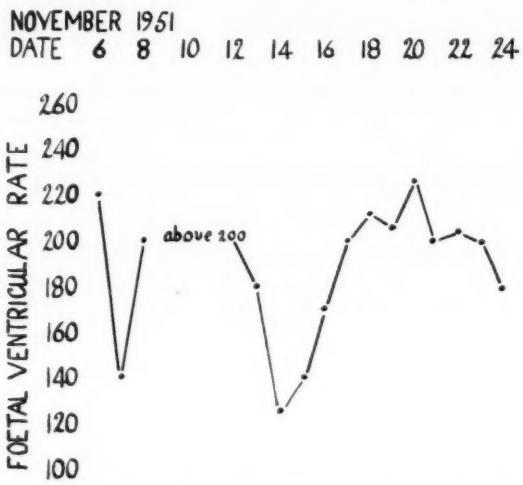


FIG. 3.—Case 2. Record of the fœtal heart rate during the last month of pregnancy.

DISCUSSION

In a study of 41 cases of paroxysmal tachycardia occurring in children under the age of 14 years, Nadas *et al.* (1952) found that 25 were under the age of four months. Of these 25 patients, only one child was a girl and 18 were without any recognizable factor to account for the tachycardia. This contrasted with the 16 children over the age of four months in whom the sexes were more equally represented and in whom an ætiological factor was frequently demonstrable. Some 16 cases (Table) have now been reported where an auricular tachycardia commenced in fœtal life. The sex incidence has been about equal (9 male, 7 female) and in only two babies has there been an associated malformation of the heart; one of these was reported by Taussig (1947) when she described a child with congenital auricular flutter associated with an auricular septal defect, the other by Siderides *et al.* (1957) who recorded the same arrhythmia occurring in association with fibro-elastosis. The difference in sex incidence between the cases of auricular tachycardia presenting in antenatal life and those occurring in children under the age of four months suggests that either the ætiology of the tachycardia differs in the two groups, or there is a tendency for the arrhythmia to be controlled spontaneously after delivery in the female child. It must be emphasized that some babies with auricular tachycardia detected first in the early months of life may have had paroxysms of tachycardia in utero, that were unrecognized, and while the total number of patients reported with auricular tachycardia remains small, dogmatic conclusions about the significance of this differing sex incidence remain unjustified.

The development of the arrhythmia in fœtal life might be determined by some physiological change occurring in utero, but this can hardly be responsible when the tachycardia recurs some weeks after birth as in Case 1. It would appear more likely that there is an underlying functional instability of the auricular muscle and that this liability is corrected as the infant matures.

Anderson and Adams (1953) have commented upon the high birth weight of the infants with congenital auricular tachycardia, but in Case 1 the high birth weight was explained by the water retention occurring during the phase of cardiac failure. The weight fell by over 2½ lb. when the

tachycardia had been controlled and the œdema had subsided. The details of the other published cases do not permit further amplification of this view.

The electrocardiographic findings in 14 cases are available for study. In 9 the diagnosis is given as auricular flutter with varying degrees of block, the remaining 5 are designated as paroxysmal tachycardia although some of the authors state that auricular flutter cannot be excluded. The difficulty in differentiation between these two disturbances of rhythm is well recognized and Evans (1944) comments on the unity of the two arrhythmias and produces some support for the view that they are in fact inseparable and that the term auricular tachycardia embraces both disturbances of rhythm.

TABLE

FŒTAL AURICULAR TACHYCARDIA

Author	Sex	Birth weight	Type	Treatment
		lb. oz.		
Carr and McClure, 1931	F	10 13½	Flutter	None
Tollas, 1933	M	?	?	None
Sherman and Schless, 1934	M	7 8	Flutter	Digitalis
Tarnower and Lattin, 1942	F	8 12	Flutter	Digitalis
Hedberg, 1945	M	8 12	Flutter	Digitalis
Garvin and Kline, 1947	F	8 1½	Supraventricular	Digitalis Quinidine
Taussig, 1947	F	?	Flutter	Digitalis
Stadler, 1948	M	7 13	Flutter	Digitalis
McLean, 1952	M	8 14	Flutter	Digitalis
Sancetta, Redding, and Haubrich, 1952	M	7 11	Supraventricular	Bilateral carotid pressure
Anderson and Adams, 1953	F	7 3	Flutter	Digitalis
Wilburne and Mack, 1954	F	7 14	Supraventricular	Digitalis
Hilrich and Evrard, 1955	M	8 4	Supraventricular	Digitalis
Siderides, Antonius, and Richlan, 1957	M	8 0	Flutter	Digitalis
Kesson	F	9 1	Supraventricular	Digitalis
	M	8 14	Supraventricular	None

On those occasions where auricular tachycardia is suspected or proved in fœtal life, the present evidence does not suggest that there should be any departure from the usual management of pregnancy or labour. Hyman (1930) made a study of the fœtal heart by phonocardiography and he detected arrhythmia in 9 per cent of his patients. The disturbances of rhythm were divisible into three groups, first those cases with sinus arrhythmia, secondly those with extrasystoles, and thirdly those showing gross irregularity of the heart rhythm. In neither group I nor II was the arrhythmia of any clinical importance, but in group III it was held to be of serious significance as 3 out of his 11 cases in this group died in utero. Hyman believed the arrhythmia was the result of auricular fibrillation and he made the suggestion that digitalization of the mother might have produced a more favourable result. This view should be accepted with reservations at present since his descriptions were necessarily incomplete and no account is taken of the possibility that the arrhythmia in the fatal cases may have resulted from terminal fœtal distress.

When the arrhythmia persists after delivery, although the tachycardia can cease spontaneously as shown by the cases described by Carr and McClure (1931) and Tollas (1933) the condition is potentially too grave to justify expectant treatment. Attempts at vagal stimulation are rarely effective in controlling the tachycardia in infancy, although Sancetta *et al.* (1952) met with success. Nadas (1952) describes a fatality that may have resulted from this procedure. Digitalis is undoubtedly the drug of choice and Garvin and Kline (1947) report the sole example where the drug failed and quinidine was required before normal rhythm was established. Digitalis must be given in full dosage, but the choice of preparation should be that which the practitioner is accustomed to use. There is little evidence to suggest that the continued administration of the

drug after normal rhythm is established will prevent a recurrence and it seems preferable to withhold the drug until the arrhythmia is again present. Although the onset of further attacks may be insidious, it is unlikely that the child would suddenly become gravely ill before therapy could be instituted.

The prognosis as far as the arrhythmia is concerned is good provided digitalis is given early and in adequate amounts. There is a risk of the recurrence of the arrhythmia but this, too, shows a good response to digitalis. In the absence of any underlying congenital malformation of the heart the arrhythmia is unlikely to reappear after the age of six months. In those cases where digitalis in adequate amounts fails to control the tachycardia, there is usually an underlying malformation of the heart, and the prognosis will depend on the nature of the structural defect.

Summary

Two cases of fœtal auricular tachycardia are recorded, and the cases previously described are briefly reviewed.

The treatment and prognosis is discussed.

References

Anderson, R. C., and Adams, F. H. (1953). *J. Pediat.*, **43**, 668.
Buckland, F. O. (1892). *Trans. Clin. Soc. Lond.*, **25**, 92.
Carr, J. G., and McClure, W. B. (1931). *Amer. Heart. J.*, **6**, 824.
Evans, W. (1944). *Brit. Heart J.*, **6**, 221.
Garvin, J. A., and Kline, E. M. (1947). *Amer. Heart J.*, **33**, 362.
Hedberg, G. T. (1945). *Acta. Obstet. Gynec. Scand.*, **25**, 392.
Hilrich, N. M., and Evrard, J. R. (1955). *Amer. J. Obstet. Gynec.*, **70**, 1139.
Hyman, A. S. (1930). *Amer. J. Obstet. Gynec.*, **20**, 332.
McLean, M. (1952). *Arch. Dis. Childh.*, **27**, 436.
Nadas, A. S., Daeschner, C. W., Roth, A., and Blumenthal, S. L. (1952). *Pediatrics*, **9**, 167.
Sancetta, S. M., Redding, T. H., and Haubrich, W. S. (1952). *New Engl. J. Med.*, **247**, 943.
Sherman, J., and Schless, R. A. (1934). *J. Pediat.*, **5**, 802.
Siderides, L. E., Antonius, N. A., and Richlan, A. (1957). *J. Pediat.*, **51**, 435.
Stadler, H. E. (1948). *J. Pediat.*, **33**, 624.
Tarnower, H., and Lattin, B. (1942). *N.Y. St. J. Med.*, **42**, 805.
Taussig, H. (1947). *Congenital Malformations of the Heart*. New York. p. 532.
Tollas, H. (1933). *Zbl. Gynak.*, **57**, 60.
Wilburne, M., and Mack, E. G. (1954). *J. Amer. med. Ass.*, **154**, 1337.

PULMONARY HYPERTENSION WITH SPECIAL REFERENCE TO THE VASOCONSTRICTIVE FACTOR*

BY

PAUL WOOD

From the Institute of Cardiology, National Heart Hospital, and the Brompton Hospital

Received July 2, 1958

The normal pulmonary blood pressure in a series of 60 normal controls studied at the Institute of Cardiology and at the Brompton hospital was 16/7 mm. Hg with reference to the sternal angle, the mean being 11 mm. and the range 8/2–28/14 mm. The mean cardiac output was 8 litres a minute, and the common range 5·5 to 10·5 litres a minute. The left atrial pressure averaged 2 to 3 mm. Hg.

The pulmonary vascular resistance, which in simple units is the pulmonary artery pressure minus the left atrial pressure in mm. Hg divided by the pulmonary blood flow in litres a minute, was therefore about 1 unit or 80 dynes sec./cm.$^{-5}$.

Definition of Pulmonary Hypertension. Pulmonary hypertension literally implies a pulmonary blood pressure above 30/15 mm. which is the upper limit of the normal range. In practice serious pulmonary hypertension usually means a pressure at or around systemic level, but rarely in excess of 150 mm.

CLASSIFICATION

There are five basic types of pulmonary hypertension as shown in the classification below, and it may help to add a sixth (polygenic), to describe cases of mixed ætiology.

Type	Definition
Passive	Raised pulmonary venous pressure
Hyperkinetic	Increased pulmonary blood flow
Obstructive	Pulmonary embolism or thrombosis
Obliterative	Reduction of pulmonary vascular capacity
Vasoconstrictive	Functional vasoconstrictive reaction
Polygenic	Arising in more than two of the above ways

Passive pulmonary hypertension is caused by any condition that elevates the pulmonary venous pressure, e.g. left ventricular failure, mitral valve disease, myxoma of the left atrium, cor triatriatum, multiple pulmonary venous thrombosis, constrictive pericarditis, and tense pericardial effusion.

Hyperkinetic pulmonary hypertension due to increased flow may occur in patent ductus, aorto-pulmonary septal defect, perforation of an aortic sinus into the pulmonary artery or right ventricle or right atrium, ventricular septal defect, perforated ventricular septum, atrial septal defect, and partial anomalous pulmonary venous drainage into the right atrium. Associated with central cyanosis it may occur in transposition of the great vessels, persistent truncus, pulmonary atresia

* The George Fahr Lecture, delivered at the University of Minnesota, U.S.A. on March 18, 1958. This lecture is a modification of the hitherto unpublished Litchfield lecture delivered to the University of Oxford on March 6, 1957.

with a large broncho-pulmonary shunt, single ventricle, single atrium, and total anomalous pulmonary venous drainage directly or indirectly into the right atrium. Acquired hyperkinetic circulatory states do not as a rule cause a sufficiently high cardiac output to raise the pulmonary blood pressure.

Obstructive pulmonary hypertension results classically from massive or multiple embolism or thrombosis, and may be acute, subacute, or chronic. Surgical ligation of a main pulmonary artery in cases of pneumonectomy provides an important obstructive component to pulmonary hypertension initiated by disease in the remaining lung. Other contributory causes include stenosis of one or more main branches of the pulmonary artery, absence of a main branch of a pulmonary artery, and compression of a main pulmonary artery from a space filling lesion such as a tumour, cyst, or aneurysm.

Obliterative pulmonary hypertension may occur at capillary, arteriolar, or arterial level. Capillary obliteration may accompany emphysema and interstitial fibrosis; occlusive disease of the arterioles and muscular arteries is usually caused by great thickening of the intima—endarteritis fibrosa. This group includes all forms of cor pulmonale in which the resistance is permanently high, schistosomiasis, disseminated lupus, periarteritis, and perhaps primary pulmonary hypertension. It may also complicate all other forms of pulmonary hypertension of sufficient duration, just as organic vascular disease complicates essential hypertension in the systemic circulation.

Vasoconstrictive pulmonary hypertension occurs in response to acute alveolar hypoxia, as first demonstrated by Liljestrand (1948). In practice this is seen chiefly when acute respiratory infections or "bronchospasm" complicate cases of chronic lung disease, and it may play an important role in neo-natal asphyxia. Certain drugs, such as phenylephrine, may also cause pulmonary vasoconstriction. Just what part vasoconstriction plays in other forms of pulmonary hypertension will be discussed later.

Polygenic pulmonary hypertension is best illustrated by cor pulmonale, when hyperkinetic, obliterative, and hypoxic vasoconstrictive factors may all operate together. Another good example is when hyperkinetic pulmonary hypertension is suddenly complicated by massive thrombosis of one of the main pulmonary arteries. But it is becoming increasingly clear that almost any form of pulmonary hypertension may become polygenic in one way or another, a point that will be elaborated subsequently.

Reactive Pulmonary Hypertension

This term may be used with advantage when it is desirable not to beg the question of ætiology. It is particularly applicable to the extreme pulmonary hypertension that may complicate cases of mitral stenosis or cases with potentially large left-to-right shunts. The word implies and is intended to imply that the high pulmonary vascular resistance in these cases is a reaction of some sort to passive or hyperkinetic pulmonary hypertension. It has been omitted from the classification because its mechanism is likely to be identified with one or more of those listed. Reactive pulmonary hypertension may well aggravate obstructive and obliterative pulmonary hypertension as well.

The most fundamental problem concerning the pulmonary circulation at the present time is the nature of this reactive pulmonary hypertension. It must be due either to the development of thrombo-obstructive or obliterative vascular disease involving the muscular arteries and/or the arterioles, or to active pulmonary vasoconstriction.

The chief object of this paper is to consider the importance of the vasoconstrictive factor.

Passive (and Reactive) Pulmonary Hypertension

Passive pulmonary hypertension implies a left atrial pressure of at least 20 mm. Hg; if the normal mean P.A.–L.A. pressure gradient of about 10 mm. is preserved, this will result in a pulmonary artery pressure of about 40/20 mm. This is the usual situation in mitral stenosis at rest. On effort,

the left atrial pressure rises sharply and may easily reach 50 mm. Hg (Fig. 1). If the cardiac output doubles and the resistance remains unchanged, the pulmonary artery pressure would then measure about 100/50 mm. That pulmonary œdema does not necessarily occur when the left atrial pressure exceeds the osmotic pressure of the plasma has been attributed to the development of an interstitial barrier between the pulmonary capillaries and the alveoli, as described by Hayward (1955). About two-thirds of all cases of critical mitral stenosis have uncomplicated passive pulmonary hypertension of this kind. They may suffer from recurrent hæmoptysis, attacks of acute pulmonary œdema, and winter bronchitis due to the high pulmonary and bronchial venous pressure, and from paroxysmal nocturnal dyspnœa, orthopnœa, and severe breathlessness on effort due to chronic interstitial œdema of the lung.

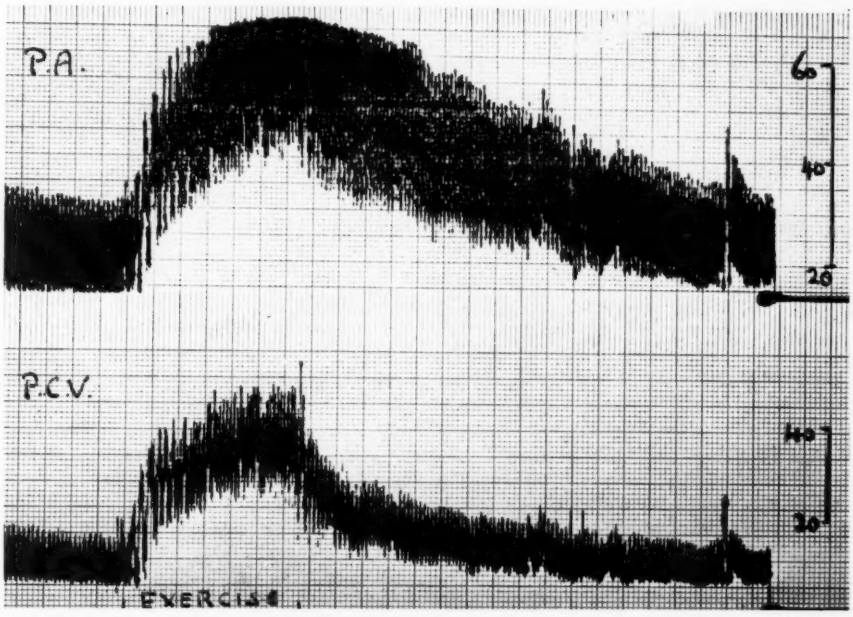


FIG. 1.—Left atrial (P.C.V.) and pulmonary arterial pressure in a case of mitral stenosis at rest and on exercise, showing passive pulmonary hypertension.

Reactive Pulmonary Hypertension in Mitral Stenosis. In about one-third of cases of critical mitral stenosis, however, the pulmonary artery pressure is raised disproportionately to the left atrial pressure, owing to an increase in the pulmonary vascular resistance. Thus in a series of 500 cases in which the mitral orifice measured between 5×3 mm. and 15×7·5 mm., the resistance was 6 to 10 units in 16 per cent and over 10 units in 12 per cent. The 60 patients with resistances over 10 units were regarded as having reactive pulmonary hypertension of the highest order and were selected for further study.

The problem was what caused the reaction? Was it the slow development of obliterative pulmonary vascular disease in response to prolonged passive pulmonary hypertension, or was it some more vital process such as reactive pulmonary vasoconstriction?

Had obliterative pulmonary vascular disease been responsible for the reaction one would have expected it chiefly in the older patients; and since a high pulmonary vascular resistance diminishes pulmonary venous congestion, one would have expected these patients to give a history of earlier

hæmoptysis, pulmonary œdema, paroxysmal cardiac dyspnœa, and orthopnœa followed by relief of these symptoms and their replacement by fatigue, hepatic pain, and œdema. In fact, however, the average age of these patients was precisely the same as the average age of those with uncomplicated passive pulmonary hypertension (39), and 80 per cent of them gave no history of pulmonary congestive symtoms at any time. A number of dramatic cases, presenting very like primary pulmonary hypertension, occurred in young women between the ages of 20 and 30. It seemed more likely, therefore, that the high resistance represented an active physiological process, and was not a late complication of passive pulmonary hypertension. The remarkable fall in resistance that followed technically successful valvotomy seemed to confirm this idea, for obliterative pulmonary vascular disease would not have been expected to behave in this way.

Demonstration of a Vasoconstrictive Factor. With the idea that the reaction might be vasoconstrictive, I decided to inject acetylcholine into the pulmonary artery thinking that it might prove a selective pulmonary vasodilator, and that a suitable dose would be destroyed by the time it reached the systemic circulation. In fact, a dose of 1 mg. injected rapidly into the pulmonary artery in a case of primary pulmonary hypertension had precisely the affect we desired: the pulmonary blood pressure fell and the systemic blood pressure rose (owing to the increase of cardiac output resulting from the fall in resistance). Since then (April, 1955) we have given acetylcholine to 16 cases of mitral stenosis, see Table I. In 8 the resistance was extreme (12 to 26 units), in 4 it was high (6 to 10 units) and in 4 it was only slightly raised (2·5 to 5 units). The technique has been described fully elsewhere (Wood *et al.*, 1957).

TABLE I

SUMMARY OF RESULTS OF ACETYLCHOLINE TEST

Conditions and type of pulmonary hypertension	Resistance (units)	No. of cases	No. in which P.A.P. fell	Av. fall in P.A. systolic pressure (mm. Hg)
Mitral stenosis				
Chiefly passive	2·5— 5	4	4	13
Partly reactive	6 —10	4	4	17
Highly reactive ..	12 —26	8	6	27
Hyperkinetic	2 — 4	3	2	5
Obstructive	—	0	—	—
Eisenmenger group				
Obliterative	15 —32			
Atrial shunt		6	0	—
Ventricular shunt ..		5	0	—
Aorto-pul. shunt ..		2	0	—
Partly hyperkinetic ..	8 —10	1	1	5
Cor pulmonale				
Polygenic	8 —15	4	3	15
Primary				
? Vasoconstrictive ..	8 —23	6	5	30

The results were fairly uniform. The pulmonary blood pressure and pulmonary vascular resistance fell appreciably, and the left atrial pressure rose (Fig. 2); the cardiac output, blood pressure, and pulse rate remained much the same. The effect was greatest in those with the highest resistances, except in two cases that did not respond at all. The average fall in resistance was from 9 to 5 units approximately.

These observations demonstrate the existence of a powerful vasoconstrictive factor in cases of reactive pulmonary hypertension secondary to mitral stenosis. The two cases that did not respond to acetylcholine were very advanced and may well have had gross secondary obliterative changes and late thrombo-obstructive lesions.

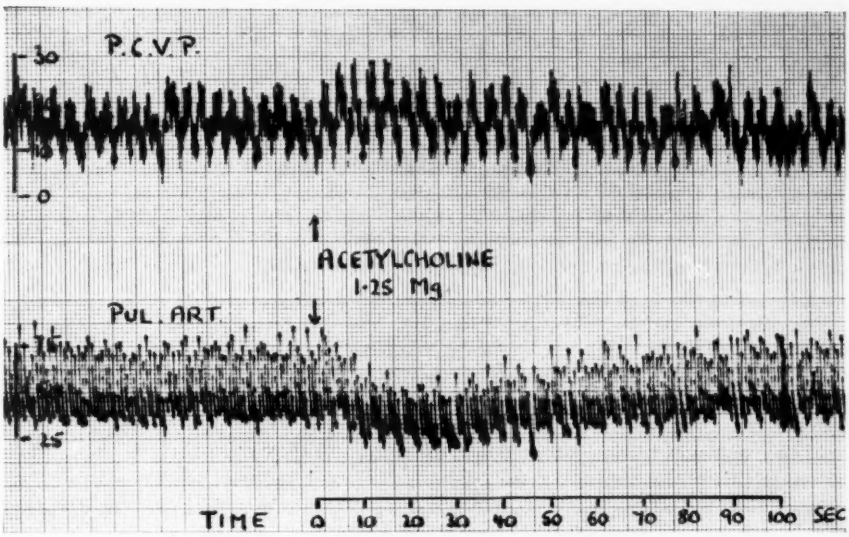


FIG. 2.—Effect of acetylcholine on the pulmonary arterial and left atrial (P.C.V.) pressure in a case of mitral stenosis with a pulmonary vascular resistance of 14 units.

HYPERKINETIC (AND REACTIVE) PULMONARY HYPERTENSION

When the pulmonary blood flow increases, the resistance falls and so prevents a rise of pressure. This holds good for normal subjects with flows up to about 16 litres a minute, which is double normal, and for resistances down to 0·5 units, which is half normal (Hickham and Cargill, 1947; Cournand, 1950). At about this level maximum pulmonary vascular capacity is reached, and any further increase of flow causes a rise of pressure. This is hyperkinetic pulmonary hypertension. It is pointed out, however, that with a flow of 24 litres a minute and a pulmonary vascular resistance of 0·5 units, the mean pulmonary blood pressure is only 12 mm. Hg with reference to the sternal angle. Flows and pressures of this order are common enough in atrial septal defect and would hardly be ranked as pulmonary hypertension. On the other hand if the resistance fails to fall and is in the upper range of normal, say 2 units, then a pulmonary blood flow of 24 litres a minute would result in a mean pulmonary artery pressure of 48 mm. Hg, which would certainly be regarded as pulmonary hypertension. Since pulmonary blood flows in excess of 30 litres a minute are rarely if ever encountered, being beyond the working capacity of the heart, it follows that hyperkinetic pulmonary hypertension implies a high normal pulmonary vascular resistance or at least failure of the resistance to fall in response to increased flow. In practice the definition of the term is usually extended to cover cases of pulmonary hypertension associated with a high pulmonary blood flow and a resistance not exceeding 4 units. Hyperkinetic pulmonary hypertension so defined often reaches systemic level.

Reactive Pulmonary Hypertension in Potentially Hyperkinetic Cases. Of particular interest are those cases with a large communication between the two circulations in which a high pulmonary blood flow is prevented by an extreme pulmonary vascular resistance more or less at systemic level (12 to 30 units). I have called this the Eisenmenger reaction, or Eisenmenger's syndrome, for it was pure chance that Eisenmenger's case happened to have a ventricular septal defect, what he described clinically being compatible with a reversed shunt at any level. It is now known that the only important factor that determines the direction of a shunt through a patent ductus or ventricular septal defect is the relationship between the systemic and pulmonary vascular resistances. The

situation in atrial septal defect is more or less similar, but there are at least seven other causes of reversed inter-atrial shunt. The problem that concerns us here is the nature of the high pulmonary vascular resistance in the Eisenmenger syndrome.

The chief hypotheses that have been advanced to explain the high resistance in these cases include congenital deficiency of the media of the muscular arteries with over-compensating endarteritis fibrosa of the intima (Gilmour and Evans, 1946), persistence of the fœtal type of pulmonary circulation with thick muscular arteries designed to maintain a high pressure (Civin and Edwards, 1950, 1951), the gradual development of obliterative pulmonary vascular disease as a complication of pulmonary plethora (the most widespread theory), and a vasoconstrictive reaction that may develop in response to severe hyperkinetic pulmonary hypertension in infancy (Wood, 1956). While it is impossible to discuss these theories adequately, evidence is offered that favours a polygenic mechanism.

Clinical Evidence

(1) In my own series the Eisenmenger reaction occurred in 16 per cent of 180 cases of patent ductus, in 25 per cent of 164 cases of ventricular septal defect, and in 8 per cent of 332 cases of atrial septal defect. As will be seen presently, this remarkable difference in frequency is attributed to the size of the defect, the length of the period in the cardiac cycle during which the shunt operates, and the swiftness with which an increased pulmonary blood flow tends to develop after birth.

(2) The size of the communication between the two circulations is very revealing. In uncomplicated patent ductus, ventricular septal defect, and atrial septal defect, it is usually 1 to 7·5 mm., 1 to 15 mm., and 3 to 8 cm. in diameter respectively. Necropsies of well-investigated cases of the Eisenmenger syndrome are rare, but by the courtesy of my colleagues I now have details of 30 such cases, 10 in each group: in these the ducts measured 7·5 to 15 mm. in diameter, the ventricular septal defects 1·5 to 3 cm., and the atrial septal defects 3 to 4 cm. across. The smallest ducts had virtually no length. It will be appreciated that the size of the communication is vital at aorto-pulmonary or ventricular level, but not at atrial level. It will also be observed that ventricular septal defects had twice the diameter of the ducts; this may be explained by the fact that a shunt through a patent ductus is potentially continuous, whereas through a ventricular septal defect it is mainly confined to systole. These facts leave no room for doubt that the Eisenmenger reaction is directly related to the potential magnitude of the pulmonary blood flow. The suggestion that the fault lies with some associated congenital anomaly of the muscular pulmonary arteries is therefore untenable, for one could hardly expect this fault to be associated only with these large defects. The anatomical data also deny that an overriding aorta has anything to do with the Eisenmenger reaction.

(3) In 103 cases of Eisenmenger's syndrome in which the level of the shunt was established physiologically with a high probability of accuracy, 28 were aorto-pulmonary, 42 ventricular, and 33 atrial (including 9 cases believed to have an ostium primum). The life histories of these cases indicated that reactive pulmonary hypertension with reversed or bi-directional shunt had been present since birth or early infancy in at least 80 per cent of those with patent ductus, and 90 per cent of those with ventricular septal defect, whereas it had been so present in a maximum of only 10 per cent of those with atrial septal defect. Thus if obliterative vascular disease is responsible for reactive pulmonary hypertension in cases of patent ductus and ventricular septal defect, it must develop remarkably quickly. Moreover, since torrential flows in atrial septal defect continue for several decades before being complicated by a high resistance (if ever), rapidly developing obliterative vascular disease of the kind postulated must be attributed to high pressure, not to increased flow. It follows that the high pressure must precede the intimal thickening, which means that obliterative pulmonary vascular disease cannot be initially responsible for reactive pulmonary hypertension in the Eisenmenger syndrome.

(4) The remarkable difference in the behaviour of cases with atrial septal defect demands some comment. In the first place it must be pointed out that the remark applies to the ordinary secundum defect, much less so to the ostium primum, which may behave like a ventricular septal defect

in respect of the Eisenmenger reaction. Thus of the 9 ostium primum cases with reactive pulmonary hypertension in the present series, all but one dated from birth or early infancy. It is suggested that a secundum type of defect may not function as such for some weeks or months after birth, because the filling resistance of the hypertrophied right ventricle should not be dissimilar to that of the left at that time, an idea expressed independently by Edwards (1957). If the right ventricle takes longer to involute than the muscular pulmonary arteries of the fœtus, then the pulmonary vascular resistance would fall to normal before an appreciable left-to-right shunt tended to keep the pressure up. As stated previously, once the resistance is normal it is extremely difficult for high flows to cause significant pulmonary hypertension.

Pathological Evidence

It is always dangerous to argue physiologically from anatomical data. A prime illustration of this axiom relating to the present subject was the belief that an overriding aorta explained Eisenmenger's complex. Nevertheless, there are certain pathological findings that may have great significance, and these must be mentioned briefly. The first of these is the hypertrophied media of the muscular arteries of the fœtus. Very similar appearances during the first two years of life in cases of Eisenmenger's complex led Edwards (1950) to postulate that it was the persistence of the fœtal type of pulmonary circulation that maintained the high pulmonary vascular resistance in the Eisenmenger syndrome and so prevented a left-to-right shunt of a magnitude that endangered life. The rapid involution of these vessels after birth, parallel with a fall in pulmonary vascular resistance, suggests that in the fœtus they are in a state of active vasoconstriction.

The second pathological finding of great significance in the Eisenmenger syndrome is the absence of obliterative thickening of the intima during the first two years of life (Edwards, 1957). This indicates that "endarteritis fibrosa" is a result rather than a cause of the Eisenmenger syndrome, and is an anatomical reaction to high pressure not to increased flow, because the latter has already been prevented in these cases.

The third important finding is that the thickened media of the muscular arteries in established cases of Eisenmenger's syndrome represent larger arteries in a state of contraction rather than smaller arteries with greatly thickened coats (Short, 1957).

Finally, the high incidence of thrombo-obstructive lesions in later life cannot be ignored.

The most likely interpretation of these pathological data is that something prevents the thick muscular arteries of the fœtus from involuting after birth, and maintains them in a state of active vasoconstriction. The agent responsible cannot be an increased pulmonary blood flow, because that is prevented by the reaction under discussion. What is more likely than that it results from pulmonary hypertension itself? With a large defect at aorto-pulmonary or ventricular level any fall in resistance would at once be met by an increase in pulmonary flow which would maintain the pulmonary blood pressure at systemic level. Only a very small hyperkinetic factor is required to maintain the pulmonary blood pressure at systemic level in the presence of a resistance of say 10 units, which is well below that in the fœtus. Reactive obliterative intimal thickening seems to develop gradually over the years, and may well slowly replace vasoconstriction as the chief means of maintaining the high resistance. Thrombo-obstructive lesions occur later still.

Physiological Observations

In an attempt to determine what part vaso-constriction might be playing in the Eisenmenger syndrome, acetyl-choline was given to 13 cases with resistances ranging between 15 and 32 units. The communication between the two circulations was atrial in 6, ventricular in 5, and aorto-pulmonary in 2. The pulmonary blood pressure did not fall primarily in a single instance (Fig. 3), even with a dose of 2 mg. It seemed possible, however, that a fall in resistance might be compensated for by increased flow without any alteration of pressure; accordingly, the arterial oxygen saturation was measured simultaneously, on the chance that it might rise, but in no instance was any such rise observed (Fig. 4). Instead, however, in some cases there was a fall (Fig. 5). This

suggested the possibility of a paradoxical response, and shortly afterwards we obtained an actual rise of pulmonary artery pressure in one case which seemed to confirm the possibility (Fig. 6). Then came a report from Adams *et al.* (1957) that acetylcholine caused pulmonary vasoconstriction in newborn babes. This seemed to clinch the matter, and in conjunction with our findings appeared to confirm Edwards' idea that the pulmonary vessels in Eisenmenger's syndrome remained fœtal in character.

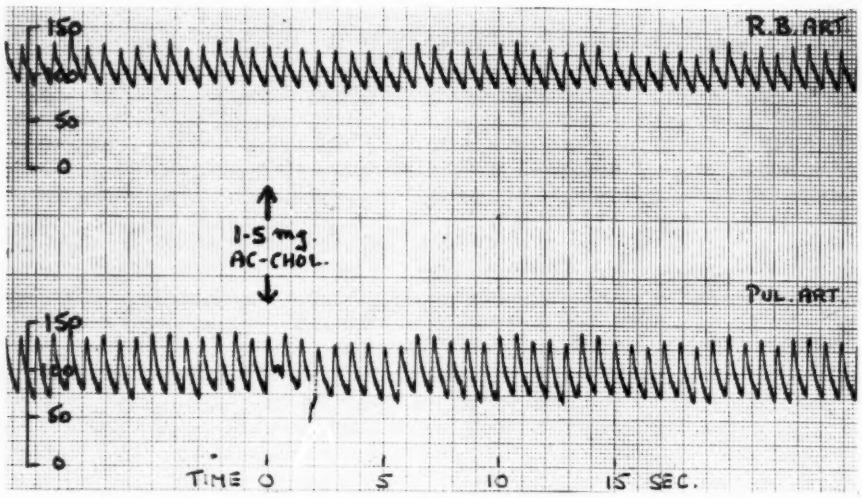


FIG. 3.—Brachial and pulmonary arterial pressure in a case of Eisenmenger's complex (with necropsy proof): acetylcholine fails to lower the pulmonary vascular resistance.

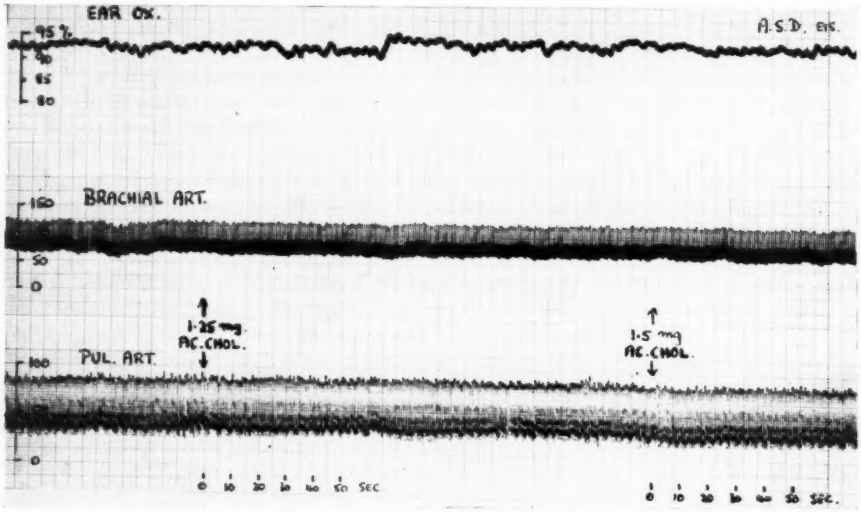


FIG. 4.—Acetylcholine also fails to raise the arterial oxygen saturation in a case of atrial septal defect with the Eisenmenger reaction.

There were two further surprises in store, however. First we found that acetylcholine lowered the arterial oxygen saturation sharply, as well as the pulmonary artery pressure, in a case of cor pulmonale, suggesting that it may open up physiologically closed vascular pathways through unventilated lung, and that this might occur to a lesser extent in any kind of patient lying quietly on a catheter table, particularly when premedicated with barbiturate. Both observation and expectation have been amply confirmed since. This means that a fall in arterial oxygen saturation

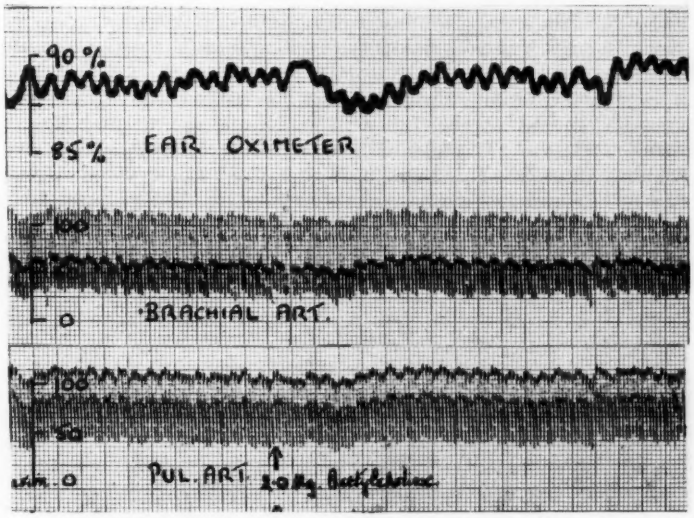


FIG. 5.—Acetylcholine injected into the pulmonary artery may lower the arterial oxygen saturation in some cases of Eisenmenger's syndrome.

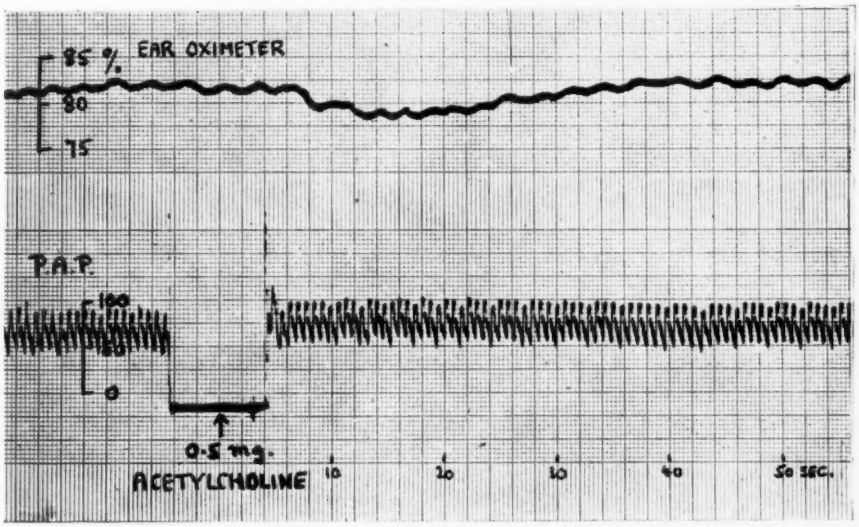


FIG. 6.—Rise of pulmonary artery pressure and fall of arterial oxygen saturation after injecting acetylcholine in a case of persistent ostium primum with the Eisenmenger reaction.

following an injection of acetyl-choline in cases of Eisenmenger's syndrome cannot be taken as evidence of an increased right-to-left shunt secondary to pulmonary vasoconstriction.

I then wrote to Dr. Geoffrey Dawes and asked him if he would be kind enough to check the effect of acetylcholine on the fœtal pulmonary circulation in animals, and he has since told me that in his first few experiments he obtained a sharp drop in pulmonary blood pressure when using a dose equivalent to ours. At the present time, therefore, the point remains equivocal.

The fact is established, however, that acetylcholine fails to lower the pulmonary vascular resistance in cases of the Eisenmenger syndrome in adults and children over 5 years old. Whether this is due to secondary obliterative pulmonary vascular disease or to an unusual physiological response remains to be seen.

It is possible to go further in one respect, however. If in the Eisenmenger syndrome one of the pulmonary arteries is stenosed, so that the pressure beyond the stricture is appreciably below systemic level, then the response to acetyl-choline delivered to that pulmonary artery is normal, the pressure falling sharply (Fig. 7). This helps to dispose of the idea that the fault in the peripheral pulmonary arteries in Eisenmenger's syndrome is congenital.

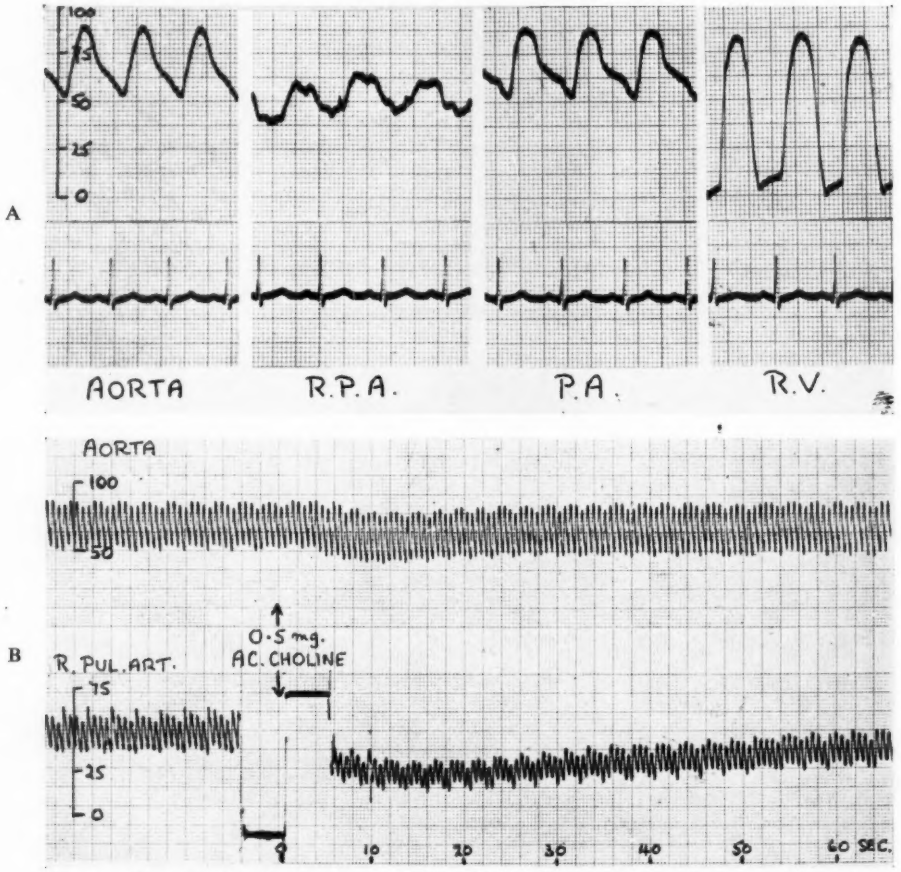


FIG. 7.—Case of aorto-pulmonary septal defect with the Eisenmenger reaction: there was moderate stenosis of the right pulmonary artery (A). Acetylcholine injected into the right pulmonary artery causes a sharp fall in pressure (B).

Obstructive Pulmonary Hypertension

It has long been known that at least two-thirds of the total cross-section of the pulmonary vascular bed must be obstructed before the pulmonary blood pressure rises (Haggart and Walker, 1923; Gibbon *et al.*, 1932). The commonest cause is massive, multiple or recurrent thrombo-embolism, and cases may run an acute, subacute, or chronic course. A thrombo-obstructive factor may also complicate any other form of pulmonary hypertension or pulmonary vascular disease.

Omitting acute cases of massive embolism, there were eight examples of subacute or chronic thrombo-embolic obstructive pulmonary hypertension in the present series. Apart from the characteristic history of phlebo-thrombosis preceding the onset, these cases presented like primary pulmonary hypertension, and if treated too late ran a similar course. Owen *et al.* (1953) described twelve typical cases.

The disease has been reproduced in animals by injecting finely fragmented fibrin clot intravenously into rabbits (Harrison, 1948). After lodging in and obstructing small pulmonary arteries, the clots gradually became organized, the lumina of the vessels became reconstituted, and marked fibro-elastic intimal thickening resulted. The end product was similar to the findings in primary pulmonary hypertension.

Successful treatment depends upon early recognition, long-term anticoagulant therapy, the administration of pulmonary vaso-dilating agents such as priscol, aminophylline, and perhaps reserpine, and a prolonged attempt to keep the pulmonary blood flow as low as possible by means of rest, dehydration, and perhaps ganglionic blocking agents (to lower the venous filling pressure). The object is to keep the pulmonary blood pressure as low as possible while the pulmonary circulation is being restored, in order to prevent secondary vasoconstrictive or obliterative vascular reactions. One of my cases that seemed beyond redemption has been cured by these means, and another has been much improved, although her pulmonary vascular resistance is still moderately raised (6 units). Acetylcholine has not been given so far to any member of this group, so we are unable to state whether there is a vasoconstrictive reaction or not.

Obliterative Pulmonary Hypertension

Widespread occlusive pulmonary vascular disease has been demonstrated repeatedly both microscopically and by radio-opaque injection methods (Short, 1957) in practically all varieties of long-standing pulmonary hypertension. As explained previously, the most likely interpretation of these findings is that they represent an anatomical reaction to prolonged stress; that they are the result rather than the cause of pulmonary hypertension. When sufficiently severe and widespread, however, there can be little doubt that they increase the resistance still further, and accelerate the down-hill course of the disease.

The most notable and best-studied example of this secondary obliterative process is that already described in the later stages of Eisenmenger's syndrome. The consistently negative response to acetylcholine in this group suggests that obliterative pulmonary vascular disease presents a solid anatomical obstruction to flow, which can no longer be influenced by vital processes. If this interpretation is correct, then the response to acetyl-choline provides a simple physiological test of the degree of such obstruction.

More or less primary obliterative pulmonary hypertension may conceivably occur in schistosomiasis, disseminated lupus, and periarteritis, but few vital physiological facts are available in these cases.

Pulmonary Hypertension in Cor Pulmonale

It is difficult to know how best to classify pulmonary hypertension in cor pulmonale, because so often it appears to be polygenic, being brought about by a combination of obliterative, hyperkinetic, and hypoxic vasoconstrictive factors.

There were 65 cases of well established cor pulmonale in the present series, and the pulmonary vascular resistance was raised, averaging 6·6 units, in 85 per cent of them; but the range was enormous, the resistance being normal (0·5 to 2 units) in 15 per cent, slightly raised (3 to 5 units) in 45 per cent, moderately raised (6 to 10 units) in 20 per cent, and extreme (over 10 units) in 20 per cent.

Hyperkinetic Factor. This was first demonstrated by Howarth *et al.* (1947), and was regarded as a compensation for hypoxia. In the present series, however, the average cardiac output was only 6 litres a minute at rest, and was very rarely above 10 litres a minute even when the resistance was low; these figures are well within the normal range for our laboratories. Since the patients with the highest pressures usually had the highest resistances and the lowest cardiac outputs, the hyperkinetic factor cannot be an important component of pulmonary hypertension in cor pulmonale.

Hypoxic Vasoconstriction. During acute infections transient alveolar hypoxia above the usual level increases the pulmonary hypertension in cases of emphysematous cor pulmonale by adding a vasoconstrictive factor, as described by Motley *et al.* (1947). It is not generally believed, however, that vasoconstriction initiated by alveolar hypoxia is maintained, for it cannot be demonstrated in chronic cases when free from infection and bronchospasm (Mounsey *et al.*, 1952).

Obliterative Factor. Elimination of both the hyperkinetic and hypoxic factors as important causes of severe pulmonary hypertension in cor pulmonale appears to leave little choice but to assume that obliterative pulmonary vascular disease is responsible. The idea that more than two-thirds of the pulmonary capillaries were obliterated in emphysema has never had much appeal, but obliteration of capillaries, arterioles, and small muscular arteries from diffuse interstitial fibrosis could well be on the grand scale.

Acetylcholine Studies. Only four cases of cor pulmonale were given acetylcholine, and each was different.

A woman with mixed emphysema and fibrosis caused by extensive old pulmonary tuberculosis responded briskly, her P.A. pressure falling immediately from 87/32 to 77/25, the systemic blood pressure rising from 122/75 to 130/80, and the cardiac output rising from 3·1 to 3·5 litres a minute.

A man with the Hamman-Rich syndrome and a pulmonary blood pressure of 60/22 responded briskly and in slightly greater degree; simultaneously his arterial oxygen saturation fell.

A man with diffuse interstitial fibrosis from sarcoid, a cardiac output of 6·7 litres a minute, P.A.P. 40/20, resistance 4 units, and arterial oxygen saturation 88 per cent, failed to respond in any way to 1·5 mg. acetylcholine.

A man with hypoxic cor pulmonale from emphysema, with a cardiac output of 3·5 litres a minute, P.A.P. 22/10, resistance 5 units, and arterial oxygen saturation 88 per cent, responded to acetylcholine by dropping his P.A.P. by 2–3 mm. Hg and his arterial oxygen saturation by about 4 per cent.

Further work must be done before any firm conclusions can be drawn, but it is clear that a vasoconstrictive factor is commonly active in a variety of forms of chronic cor pulmonale, that it may particularly involve vascular pathways through poorly ventilated lung, and that diffuse interstitial fibrosis of at least one kind (sarcoid), may cause purely obliterative pulmonary hypertension in which no vasoconstriction can be demonstrated.

Primary Pulmonary Hypertension

The present series included 26 cases of primary pulmonary hypertension, 21 of them being female, between the ages of 9 and 48. The diagnosis has already been confirmed at necropsy in 17 of them, and so far there have been no diagnostic errors one way or the other. The clinical and pathological picture of this obscure disease has been described too often, and there is no point in belabouring it further. What is needed is more evidence concerning possible ætiological agents, and more light on early physiological behaviour.

Very suggestive is the work of Barnard (1954), who produced a form of intimal endarteritis fibrosa in mice and rabbits by injecting thrombo-plastin intravenously, so that fibrin emboli were

formed *in vivo*. The end results of these experiments were virtually indistinguishable from those of primary pulmonary hypertension in man.

There can be no doubt that chronic thrombo-embolic pulmonary hypertension imitates primary pulmonary hypertension very closely, apart from the history of initial phlebo-thrombosis. But there are two differences that must not be ignored. Of my 8 severe and unquestionable thrombo-embolic cases imitating primary pulmonary hypertension, 5 were men, despite the female sex bias given to this condition by phlebo-thrombosis complicating pregnancy, as in the well-documented case described by Castleman and Bland (1946). Secondly, primary pulmonary hypertension may begin in childhood, as in 3 of my 26 cases: if these are thrombo-embolic the intravascular clotting must be of a very unusual kind.

Acetylcholine Studies. Six cases of primary pulmonary hypertension were given acetylcholine. A profound fall of pulmonary blood pressure (averaging 30 mm. Hg systolic) and resistance was recorded in five of them; simultaneously the systemic blood pressure and cardiac output rose (Fig. 8). The magnitude of the response was unsurpassed in any other condition. There can be no doubt, therefore, that a powerful vasoconstrictor factor is commonly present in these cases, which at once distinguishes them from members of the Eisenmenger group. Since two of them had had the condition for 8 and 4 years respectively, long enough for secondary obliterative changes to have

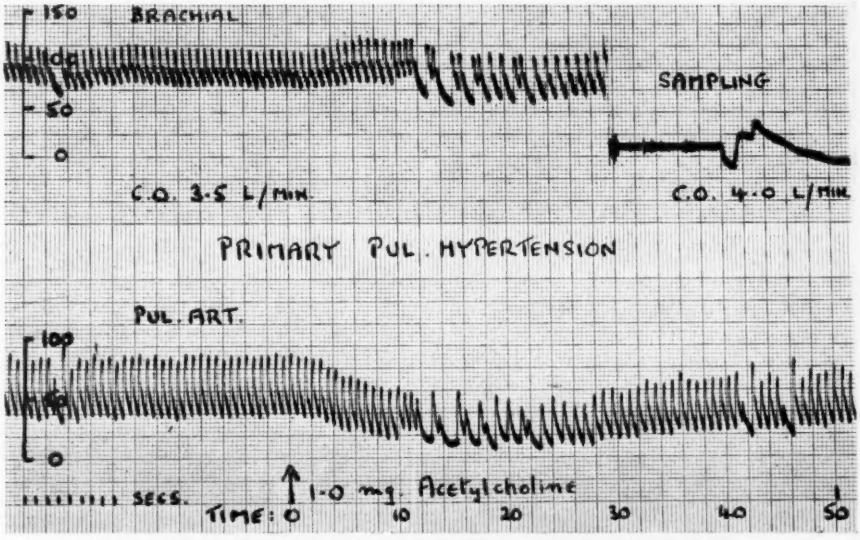


FIG. 8.—Effect of acetylcholine in a case of primary pulmonary hypertension.

developed, this difference in behaviour is all the more remarkable, and may well prove of fundamental significance.

In two cases of primary pulmonary hypertension the vasoconstriction was also relieved by aminophylline and priscoline, as demonstrated by Dresdale (1951). Therapeutically, however, these drugs proved valueless.

SUMMARY AND CONCLUSIONS

A working classification of pulmonary hypertension is offered.

The mechanism of the chief varieties of pulmonary hypertension is discussed.

Acetylcholine has proved to be an excellent selective pulmonary vasodilator, and a useful tool with which to probe all forms of pulmonary hypertension in order to determine the degree of

physiological vasoconstriction present. A maximum response includes a fall in pulmonary blood pressure and pulmonary vascular resistance, a rise in left atrial pressure (in mitral stenosis), cardiac output, and systemic blood pressure, and a fall in arterial oxygen saturation (especially in cor pulmonale).

The results are summarized in the Table and show that active vasoconstriction is strongest in primary pulmonary hypertension and in reactive pulmonary hypertension from mitral stenosis; it is present in some degree, however, in almost all forms of pulmonary hypertension except the Eisenmenger syndrome, in which it is consistently absent—at any rate in children over 5 years old.

The cause of the vasoconstriction has not yet been proved, but it is again suggested that it may well be a reaction to a high pulmonary blood pressure itself. However pulmonary hypertension is initiated, reactive vasoconstriction seems to aggravate and maintain it, and so closes a vicious circle.

Obliterative pulmonary vascular disease seems to develop gradually over the years in all forms of pulmonary hypertension, and also serves to aggravate and maintain the high resistance. Secondary thrombo-obstructive lesions develop later still.

The absence of demonstrable vasoconstriction in the Eisenmenger group may be due to secondary obliterative pulmonary vascular disease or possibly to an abnormal physiological response to acetylcholine on the part of vessels having fœtal characteristics. No information is yet available concerning the effect of acetylcholine on the pulmonary vascular resistance of infants under two years of age with the Eisenmenger syndrome.

References

Adams, F. H., Lind, J., and Rauramo, L. (1957). *Abstracts of Papers 30th Sc. Sessions of Amer. Heart Ass., Oct.* 25–28. Chicago.

Barnard, P. J. (1954). *Brit. Heart J.*, **16**, 93.

Castleman, B., and Bland, E. F. (1946). *Arch. Path.*, **42**, 581.

Civin, W. H., and Edwards, J. E. (1950). *Circulation*, **2**, 545.

—— (1951). *Arch. Path.*, **51**, 192.

Cournand, A. (1950). *Circulation*, **2**, 641.

Dresdale, D. T., Schultz, M., and Michtom, R. J. (1951). *Amer. J. Med.*, **11**, 686.

—— (1947). *Amer. J. Physiol.*, **150**, 315.

Edwards, J. E. (1950). *Proc. Inst. Med., Chicago*, **18**, 134.

—— (1957). *Circulation*, **15**, 164.

Gibbon, J. H., Hopkinson, M., and Churchill, E. D. (1932). *J. clin. Invest.*, **11**, 543.

Gilmour, J. R., and Evans, W. (1946). *J. Path. Bact.*, **58**, 687.

Haggart, G. E., and Walker, A. M. (1923). *Arch. Surg.*, **6**, 764.

Harrison, C. V. (1948). *J. Path. Bact.*, **60**, 289.

Hayward, G. W. (1955). *Brit. med. J.*, **1**, 1361.

Hickam, J. B., and Cargill, W. H. (1948). *J. clin. Invest.*, **27**, 10.

Howarth, S., McMichael, J., and Sharpey-Schafer, E. P. (1947). *Clin. Sci.*, **6**, 187.

Liljestrand, G. (1948). *Arch. intern. Med.*, **81**, 162.

Motley, H. L., Cournand, A., Werko, L., Himmelstein, A., and Dresdale, D. (1947). *Amer. J. Physiol.*, **150**, 315.

Mounsey, J. P. D., Ritzman, L. W., Selverstone, N. J., Briscoe, W. A., and McLemore, G. A. (1952). *Brit. Heart J.*, **14**, 153.

Owen, W. R., Thomas, W. A., Castleman, B., and Bland, F. (1953). *New England J. Med.*, **249**, 919.

Short, D. S. (1957). *Lancet*, **2**, 12.

Wood, P. (1956). *Diseases of the Heart and Circulation.* 2nd ed., Eyre & Spottiswoode, London.

——, Besterman, E. M., Towers, M. K., and McIlroy, M. B. (1957). *Brit. Heart J.*, **19**, 279.

CASE REPORTS

DOUBLE-BARRELLED AORTA WITH BACTERIAL ENDARTERITIC VEGETATIONS

BY

G. L. ROBINSON

From the Dreadnought Seamen's Hospital, Greenwich

With the rising incidence of dissecting aneurysm of the last few decades (Maniglia and Gregory, 1952), valve-like arterial artefacts are likely to increase, and upon some tapping edge, sooner or later, bacterial vegetations might be expected. Such a case is here reported, apparently for the first time.

Case History

A male wood-machinist, aged 45, became febrile after a single dose of penicillin given at the end of a course of arsenical injections in a clinic for venereal disease, and was admitted to hospital in April, 1951. In 1945 he had begun to sleep upright in bed and thereafter attacks of breathlessness and tachycardia were increasingly frequent. He also felt that his memory was deteriorating. On examination, he was dyspnœic with congestion of neck veins, pulse of 168 a minute and blood pressure of 160/115. Systolic and aortic diastolic murmurs were heard. Wassermann and Kahn reactions negative. Blood counts: hæmoglobin, 13·4 g. per 100 ml., white cells, 8400 per cu. mm. Blood culture sterile. The electrocardiogram showed paroxysmal tachycardia. During treatment the rhythm reverted through fibrillation to normal. At the same time a systolic thrill became palpable, from which it was concluded that aortic stenosis must be added to the original diagnosis of aortic regurgitation, and that the cause must be rheumatism not syphilis.

He was henceforward in and out of hospital at intervals of a few months until his death in July, 1953. Signs of an infective process first appeared on his fourth admission in September, 1952, when he was delirious and sweating, had a white cell count of 11,000 per cu. mm., and gave a growth of *Streptococcus viridans* in blood culture. On treatment, the patient became mentally normal and began putting on weight within a fortnight, but relapsed and was treated in another hospital where *Streptococcus viridans* was again isolated from the blood. Presence of an aortic aneurysm was noted in the chest film at this time. He was transferred to us again in March 1953. A large abscess of sterile pus in the right thigh had to be opened during the eleventh week, and in the seventeenth week the patient died suddenly.

Necropsy

The heart showed great left ventricular hypertrophy and weighed 666 grams, the left ventricle being 23 mm., the right 4 mm. thick. The aortic cusps were thicker than normal, though still fairly flexible, and slightly shortened by fusion of their ends, with a calcified nodule in one angle. A tear in the inner wall (Fig. 1), which was sharply defined but with the edge rounded off by healing, ran spirally upward round the ascending aorta from just above the right coronary orifice to a point 5 cm. distal to the commissure. Anteriorly the two step-like edges of the tear had retracted to leave a bare area 2 cm. wide floored by re-endothelialized outer coat, with which they had fused. Posteriorly and to the right the separated inner layer of intima-media (6 cm. from side to side) was extended across the centre of the aortic lumen, while deep to it a free blood channel, nearly equal in capacity to that of the aorta itself, had been formed. This channel was re-endothelialized, though the deep surface of the separated lamina bore fibrous tags, the largest of which (up to 8 mm. long × 1 mm. diam.) stretched across the angle of separation from the rest of the wall on the right side like a strut, resembling one of the chordæ. A tear in the inner wall of the aortic arch formed the distal end of the aneurysmal passage (Fig. 2), which was between 6 and 7 cm. long. This second orifice, by which the blood returned to the main aorta, was situated between the openings of innominate and left common carotid arteries, while, at its lower and slightly less advanced end, there was

a depressed area (1 cm. diameter) of retraction and re-endothelialization similar to the larger area described in the ascending aorta. The free edge (5 cm. long) was the site of smooth firm yellow nodular projections (streaked by a little red clot) with numerous small glistening translucent granules situated on the deep (outer) surface of the edge opposite the re-endothelialized media of the main wall. The spleen (335 g.) contained the scar of an old infarct (2·5 cm. diameter). A bullet-ended thrombus was loose in the right common iliac vein. Arachnodactyly was absent.

FIG. 1.—Ascending aorta, showing separated intimal-medial layer throwing its shadow on the channel outside it.

Microscopic sections showed only the changes attributable to trauma in the ascending aorta, while the distal flap of the aneurysm was seen to consist of dense hyaline tissue, in one place calcified, covered by endothelium to which small fibrin plugs were adherent in places. Beneath one of these latter a very few coccal forms were found. *Streptococcus viridans* was grown *post mortem* both from a vegetation and from the spleen.

Discussion

The reverse process to that described here, namely the formation of aortic dissecting aneurysm from bacterial endocarditis of the aortic valve ulcerating the commissure, has been described (Bartol *et al.*, 1943), and two traumatic aneurysms of the femoral artery, one gunshot (Lipton and Miller, 1944) and one stab wound (Heckler, 1952), have developed the vegetations of bacterial endarteritis. The term "double-barrelled aorta" occurs in the description (Levine *et al.*, 1951) of a dissecting aneurysm of some five months' duration which split the ascending aorta of a thirty-eight-year-old man. The heart (740 grams) had a hypertrophied left ventricle, and a transverse tear 2 cm. above the aortic valve opened into a bulging aneurysmal sac traversed by strands of fibrous tissue and filled by blood clot.

FIG. 2.—Distal end of the aneurysmal channel shown by glass tube passing behind flap bearing vegetations of subacute bacterial endocarditis. (Cut for micro-section closed by stitches.) The dark colour of the upper part is due to adherent clot.

A case of double-barrelled aorta of fifteen years' duration in a young athlete with a grossly hypertrophied heart (860 grams), who died of cardiac failure at the age of 32, was recorded by Hall (1926). The aneurysmal tunnel, completely endothelialized, originated in an annular tear 1 cm. distal to the aortic valve and broke back into the main lumen by another annular tear at the site of a patent ductus arteriosus. The lesion occurred after running a mile race; and the evidence here, as in certain other cases where the ventricle was hypertrophied, might be taken to suggest that tears at the pericardial anchorage of the ascending aorta could be due to abnormally forceful ventricular movements, combined with an unluckily placed patch of atheroma, rather than to medial disease. Since histological degeneration is always found in the neighbourhood of aneurysmal dissections, as was pointed out (Erdheim, 1930) in the original description of medio-necrosis aortæ idiopathica cystica, it is not easy to separate effect from cause.

The present case seems almost a replica of Hall's, with the addition of bacterial vegetations on the distal end of the tunnel, and with the origin of the hypertrophied ventricle in a rheumatic incompetence instead of a congenital defect. In this case the force of the heart beats was one of the patient's complaints—a feature that might prove of some help in the discrimination of future cases. For instance, in a recent report of an ascending aortic dissection with the common termination of hæmopericardium (Bingle, 1957) the heart beats are mentioned as shaking the bed. The dissecting aneurysm seems likely to have occurred before our patient's first admission here (two years before his death) and might have been the cause of his admission to another hospital three years before that. The development of bacterial endarteritis can be reasonably assigned to the period between his third and fourth admissions, proving fatal therefore in about ten months.

Summary

A case is recorded in which a dissecting aneurysm of the ascending aorta ruptured back into the aortic arch, where the free edge of the tunnel became the site of subacute bacterial vegetations.

I should like to thank Dr. Ronald Hartley, under whose care this patient was admitted.

References

Bartol, G. M., Edwards, J. E., and Lamb, M. E. (1943). *Arch. Path.*, **35**, 285.
Bingle, J. (1957). *Brit. med. J.*, **1**, 629.
Erdheim, J. (1930). *Virchow's Archiv.*, **276**, 187.
Hall, E. M. (1926). *Arch. Path.*, **2**, 41.
Heckler, G. B., and Tikellis, I. J. (1952). *J. Amer. med. Ass.*, **150**, 1301.
Levine, E., Stein, M., Gordon, G., and Mitchell, N. (1951). *New England J. Med.*, **244**, 902.
Lipton, S., and Miller, H. (1944). *J. Amer. med. Ass.*, **126**, 766.
Maniglia, R., and Gregory, J. E. (1952). *Arch. Path.*, **44**, 298.

MYXOMA OF THE LEFT AURICLE WITH DIRECT PRESSURE TRACINGS

BY

JOHN R. H. TOWERS AND C. P. NEWCOMBE

From the General Infirmary at Leeds

Cardiac myxoma has been reported with increasing frequency in recent years. Pritchard (1951) reviewed some 200 cases then reported. At least twenty-eight further examples have been published in Great Britain and the United States of America; of these nineteen were in women and two-thirds of them died between the ages of thirty and sixty years.

Straus and Merliss (1945) attempted to estimate the true incidence by comparing the statistics of the American Medical Association for the number of autopsies performed in the United States of America with the number of cases of primary cardiac tumour reported in the same five-year period, 1938–42. The autopsies numbered 480,331 and 8 cases of primary cardiac tumour were found, giving an estimate of 17 per million. This may be regarded as a minimum figure and is equivalent to about 10 patients per annum in Great Britain.

We report a case that exhibited most of the characteristic clinical features. Few of the published accounts have included intra-cardiac pressure measurements, and none has been found in which, as in this instance, direct measurement of the left auricular pressure was made by means of a needle passed through the left bronchus.

Case Report

The patient, a Jew, was aged 45. He was first admitted to the General Infirmary at Leeds in April, 1951, with a vague history of intermittent dizziness of several months duration, followed by the sudden onset of right frontal headache and impaired vision three days previously. There was no history of rheumatic fever and no cardiac symptoms were present, but an apical presystolic murmur was queried. The blood pressure was 120/80. He was found to have a homonymous, roughly quadrantic defect of the upper left visual field which afterwards persisted.

Effort dyspnœa began early in 1954 and in June of that year there were two episodes of sudden dyspnœa followed by cough and white frothy sputum. He was examined then and found to have presystolic and systolic murmurs at the apex. He had sinus rhythm, a blood pressure of 120/85, and fine râles at both bases but no œdema. He was admitted to hospital for a month and improved readily on routine treatment. At that time fluoroscopy showed considerable left auricular enlargement with some right ventricular hypertrophy and pulmonary congestion, and the X-ray examination was considered to be in keeping with the diagnosis of mitral stenosis. The electrocardiogram showed sinus rhythm and right axis deviation only.

From this time dyspnœa became progressively worse. Œdema appeared in July, 1955, and increased steadily. In that month he lost consciousness suddenly when sitting in a chair, fell to the floor, and was unconscious for a quarter of an hour. A similar but very short loss of consciousness occurred in December, 1955. He was admitted to the Herzl Moser Hospital at Leeds in November, 1955, for treatment of congestive heart failure, and discharged nine weeks later somewhat improved, but still in failure.

In January, 1956, he was admitted to the General Infirmary at Leeds for further investigation and possible valvotomy. The physical examination showed sinus rhythm with multiple extrasystoles and a blood pressure of 115/70. The apex was in the fifth space in the anterior axillary line with a tapping cardiac impulse. The first sound was accentuated at the apex and a third sound was present in early diastole. There was a moderate, grade 3, apical systolic murmur and soft rumbling mid-diastolic and presystolic

murmurs. The sounds in other areas were normal. There were a few basal crepitations. The jugular pressure was not raised, but there was a little sacral œdema, and a smooth firm hepatic enlargement to three fingers breadth below the costal margin.

Fluoroscopy showed much the same general contour as in 1954 but with a considerable increase in left auricular and right ventricular enlargement, and it was thought that the left ventricle might also be enlarged. Again the picture was thought to be in keeping with rheumatic mitral disease. Electrocardiography now showed marked right ventricular hypertrophy. Auricular fibrillation developed in February, 1956. Left auricular and pulmonary artery pressure tracings were taken in March (Fig. 1 and 2), and showed a pulmonary artery pressure of 106/54 mm. Hg and a left auricular pressure of 61/20 mm. Hg. The left auricular tracing appeared to show considerable incompetence although the shape of the curve was unusual. He died suddenly two weeks later.

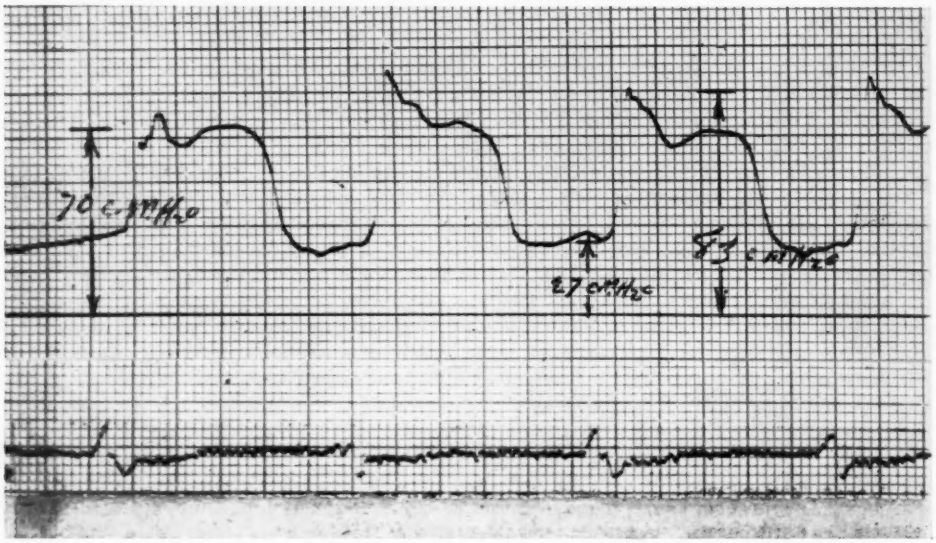


FIG. 1.—Left auricular pressure tracing taken in a case of myxoma of the left auricle, showing pressure of 61/20 mm. Hg.

Necropsy Findings

The heart weighed 560 g. The left atrium was enlarged and occupied by a large polypoid tumour mass, 9·5×6×5·5 cm., attached by a short narrow pedicle to the inter-atrial septum just below the fossa ovalis (Fig. 3). The tumour was greyish yellow, smooth, and elastic, with a transverse annular groove corresponding to the mitral ring. Old and recent hæmorrhages were apparent in the substance of the tumour, the latter being particularly notable in the apex of the tumour which projected through the mitral valve. There was no evidence of rheumatic heart disease. The right ventricle was moderately dilated and hypertrophied. The right coronary artery was completely occluded 4 cm. from its origin, and the other coronary vessels displayed patchy atheroma.

A number of small pale infarcts were present in both kidneys. There were old areas of softening in both occipital lobes of the cerebrum and in the left lobe of the cerebellum.

Discussion

Successful removal of a cardiac myxoma has only recently been reported, (Chin and Ross, 1957). A number of attempted removals had previously been described but had been unsuccessful, in

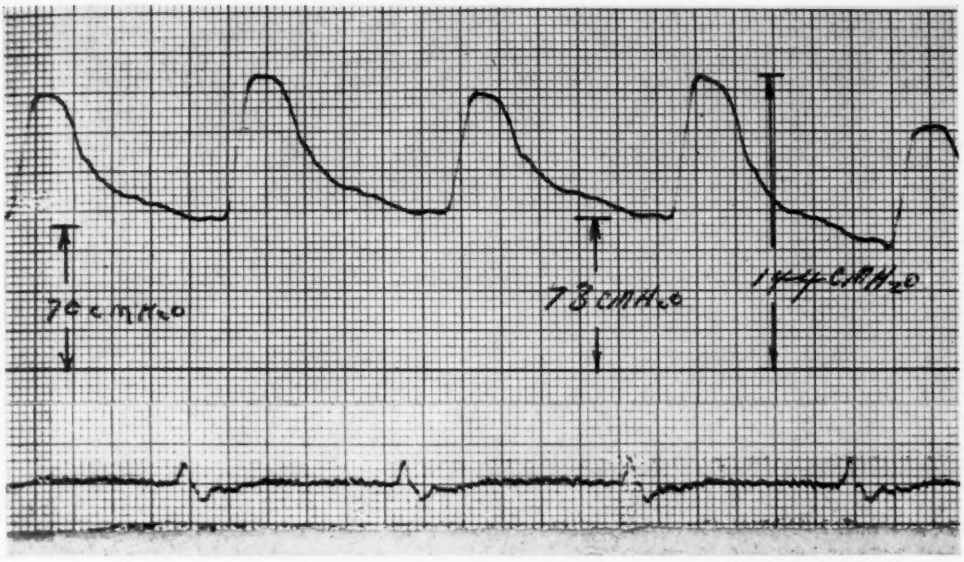


FIG. 2.—Pulmonary artery pressure tracing, showing pressure of 106/54 mm. Hg.

some cases owing to the friability of the tumour and the production of massive embolism. Nevertheless, treatment is clearly surgical as the natural history is uniformly gloomy, survival rarely exceeding eighteen months from the onset of dyspnœa.

Myxoma of the left auricle clinically simulates mitral valvular disease very closely and there are no distinguishing features upon which complete reliance may be placed. The possibility should be considered when the history is short, the course is rapid and relentless, and the response to medical treatment poor. Arrhythmias are uncommon and late. Radiologically left auricular enlargement remains slight or moderate when failure is severe. Alteration in physical signs with posture is observed in about half the cases, and sudden attacks of dyspnœa, cyanosis, præcordial pain, and tachycardia may occur. Embolic phenomena are frequent and may, as in this case, precede other evidence of cardiovascular disease.

Clinical diagnosis is, however, very rare; probably because the possibility is not considered. Kirkeby and Leren (1952) were able to make the diagnosis in their case on the basis of changing murmurs, but only in the last forty-eight hours of life.

The electrocardiogram gives little assistance in the diagnosis although the comparatively rapid development of the electrocardiographic pattern of right ventricular hypertrophy was notable in this case. In the left auricular pressure tracing several features were of interest. The rise of systolic pressure was very rapid, the *c* wave was higher than the *v* wave, and the *x* descent was well preserved; in these respects the tracing differed from those commonly seen in rheumatic mitral regurgitation and in retrospect may have been produced by a ball-valve action of the protruding portion of the tumour in the mitral orifice. In addition, the pressure in the left auricle was very high but enlargement of the left auricle was only moderate, unlike rheumatic mitral regurgitation where the left auricle is usually considerably enlarged and the pulmonary artery and left auricular pressures are not extreme. Some of these features may prove to be of diagnostic value.

When the diagnosis has been suspected, angiocardiography has usually been successful in demonstrating the tumour (Bahnson and Newman, 1953; and Steinberg *et al.*, 1953).

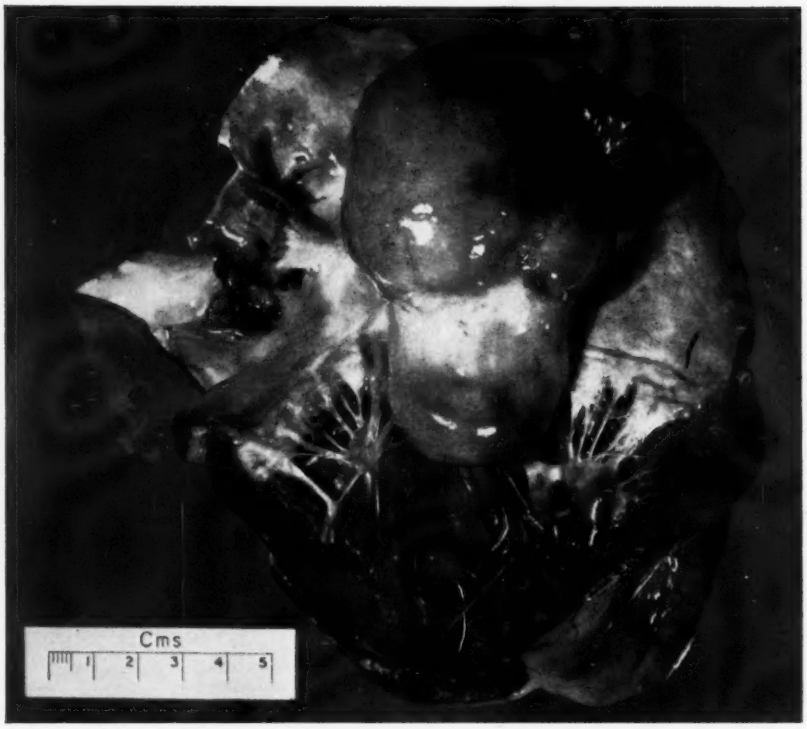


FIG. 3.—The enlarged left auricle is laid open to show a large polypoid myxoma attached by short pedicle to the inter-auricular septum.

Summary

We report a case of myxoma of the left auricle in which there were features of special interest.

The presenting symptoms and signs were those of embolism, preceding by three years the onset of dyspnœa. Recurrent dyspnœa of great severity eighteen months prior to death was followed by progressive failure, little influenced by therapy. Auricular fibrillation was delayed until two months before death.

Left auricular pressure and pulmonary artery pressures were measured by the transbronchial route, and were very high, the figure in the pulmonary artery being 106/54 mm. Hg, and in the left auricle 61/21 mm. Hg.

The tumour contained recent hæmorrhages especially in that part which projected into the left ventricle, possibly resulting in complete occlusion of the mitral orifice.

We are indebted to Mr. G. H. Wooler for the transbronchial pressure measurements, and to Dr. H. Thompson for the report on the necropsy.

References

Bahnson, H. T., and Newman, E. V. (1953). *Bull. Johns Hopkins Hosp.*, **93**, 150.
Chin, E. F., and Ross, D. N. (1957). *Brit. med. J.*, **1**, 1447.
Kirkeby, K., and Leren, P. (1952). *Acta. med. Scand.*, **143**, 385.
Pritchard, R. W. (1951). *Arch. Path.*, **51**, 98.
Steinberg, I., Dotter, C. T., and Glenn, F. (1953). *Dis. Chest*, **24**, 509.
Straus, R., and Merliss, R. (1945). *Arch. Path.*, **39**, 74.

J. G. EMANUEL

Joseph George Emanuel, an original member of the Cardiac Club, died in the Queen Elizabeth Hospital on March 3, 1958, at the age of 86. He was born on June 4, 1871, the eldest son of the Rev. G. J. Emanuel, Minister of the Birmingham Hebrew Congregation. He was educated at King Edward's School, Birmingham, and at Mason's and Queen's Colleges, the predecessors of Birmingham University and its Faculty of Medicine. He graduated B.Sc. London, in 1891 and after qualifying in 1896 held resident posts in several London hospitals. He sailed to Australia and back in 1897–98, as medical officer in a sailing ship, an experience that was unusual even in those days and one that made a deep and lasting impression on him. He was fond of recounting how he gained a reputation—not for treating a sailor seriously injured in a storm, with no assistance and very inadequate equipment, while almost prostrate with sea sickness; but for the anxious care with which he looked after the cook to whom he had inadvertently given an overdose of calomel.

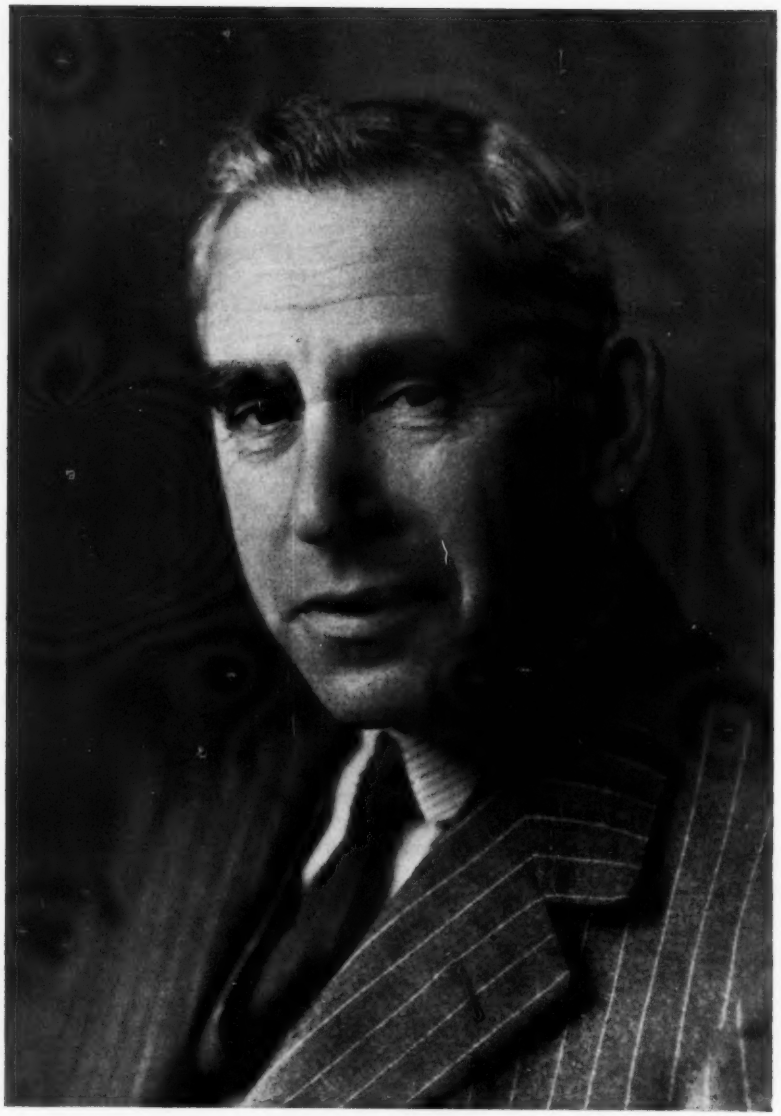
After his return to England, he became R.M.O. at the City of London Hospital for Diseases of the Chest for eighteen months until, in 1900, he finally returned to Birmingham, first as Resident Pathologist at the General Hospital. He obtained the M.R.C.P. in 1902 and the M.B., B.Ch. of the recently founded Birmingham University in the same year.

He became Physician to Out-Patients of the Queen's Hospital, Birmingham, in 1902 and Physician in 1909, and was appointed to the Children's Hospital in 1904. During the 1914–18 war, he was a captain in the R.A.M.C. and served in France with the 56th General Hospital, after which he returned to his hospital and consulting practice. He was elected F.R.C.P. in 1921.

His medical interests were wide, and his early publications were concerned with a wide variety of subjects, and even to the end he regarded himself as a general physician with a special interest in heart disease. He was fortunate in spending his professional life during a period when, the foundations of morbid anatomy having been laid, a tremendous burst of new techniques, new ideas, and new discoveries began to transform the art of medicine into a science, a process of which Emanuel approved, though with some reservations. He witnessed the birth of radiology and serology, and introduced into Birmingham the use of the Widal reaction and of dyes for the differential staining of blood cells. Later he took up with enormous zest the new techniques introduced by Mackenzie and Lewis, and was for many years the only physician in the Midlands who understood the mysteries of the polygraph and electrocardiograph. Most of his later papers were concerned with the cardiac arrhythmias.

He gave the Ingleby Lectures at Birmingham University on auricular fibrillation in 1925. In addition to a useful review of what was known about it, he analysed the activity of the patient at the moment this rhythm started and concluded that as a rule its onset was not influenced by what the patient was doing at the time.

The retiring age for physicians at the Hospital was then 60, and he reached this age in June 1931, while still at the height of his powers. He continued, however, as Joint Professor of Medicine—a post to which he had been elected in 1930—for another three years, and with a busy consulting practice for several years after, so that he had practiced in Birmingham as a consulting physician for more than half a century. He remained deeply interested in the affairs of the Birmingham Teaching Hospitals, and served on their committees for many years. He kept his interest in new ideas after his retirement, and watched with interest, though perhaps with slight disapproval, the development of physiological methods in cardiological investigation. He regularly attended the meetings of the Cardiac Society until he was nearly 80, and occasionally after that. The esteem and



J. G. EMANUEL

affection in which he was held by his colleagues was shown by his election to the Presidency of the Association of Physicians in 1939.

It is not for great discoveries that Emanuel will be remembered: the great influence he exerted was due to the force of his teaching and the sweetness and essential goodness of his character. He always listened patiently to what his colleagues and students had to say, and would consider it from every imaginable point of view (some that, we thought, nobody but Emanuel could imagine!), and this sometimes made him appear slow and hesitant. If the idea appeared valid, he would warmly and generously accept it, even if contrary to his previous views; but if not, a simple and seemingly innocent question would expose any superficiality of thought, though he asked this gently and without derision. He was a model of kindness, politeness, and consideration for his patients. He exacted the highest standards from his subordinates and would not tolerate shoddy work: to work for him was not easy, but a great experience. Very many of his house physicians remained his friends for life.

In his personal relations he was the essence of friendliness, kindness, and open-handed but unobtrusive generosity. Many people came to him for advice and help, and none went empty away. No trouble was too great for him to take on behalf of those who needed his help. He was diffident and humble, with no trace of assertiveness in his make-up. If his rise had depended on trampling on others weaker than himself, he would never have risen.

In spite of his contemplative temperament, he had great physical energy. He and his gracious wife, whose sudden death in 1951 was so crushing a blow to him, were members of the Midland Association of Mountaineers, and did a great deal of climbing in North Wales, the Alps, and the Pyrennees. Even in his eighties he scorned to travel any distance less than three miles except by brisk walking. The amputation of a foot in 1956 finally deprived him of this pleasure, but he still remained interested in his garden, his hot-house carnations, and his wide circle of friends. To the end he retained his clearness of mind and his kindness and consideration for others. He died honoured and mourned by all who knew him.

He married Ethel, a daughter of Dr. Alfred Wolff. Their only child, Richard Emanuel, is a member of the British Cardiac Society.

O. BRENNER

PROCEEDINGS OF THE BRITISH CARDIAC SOCIETY

The THIRTY-SEVENTH ANNUAL GENERAL MEETING of the British Cardiac Society was held at the Riley Smith Hall, Leeds University, on Thursday and Friday, April 17 and 18, 1958. The President, MAURICE CAMPBELL, took the Chair at 9.0 a.m. during Private Business, before handing over to the Chairman, JOHN TOWERS. 142 members and 16 visitors were present.

PRIVATE BUSINESS

1. The Minutes of the last Autumn Meeting, having been published in the Journal (**20**, 290, 1958) were taken as read and confirmed.
2. The Balance Sheet for 1957–58 was presented, having been audited and found correct by Bain and Oram. The credit balance on March 31, 1958, was £633 2*s*. In addition the Society held £800 2½ per cent Savings Bonds 1964/67.
3. Sir Henry Dale, O.M., was elected and acclaimed an *Honorary Member* of the Society.
4. Langley, McDowall, Morgan, Rennie, and Price Thomas were elected *Extra-Ordinary Members* of the Society.
5. Brenner and Holmes Sellors were elected *Members of the Council* in place of Brock and Morgan Jones (term of office expired).
6. The following Associate Members were elected as *Ordinary Members*:

J. M. Bishop
J. A. Cosh
T. D. V. Lawrie
W. Lister
K. G. Lowe
I. K. R. McMillan
R. E. Steiner
O. L. Wade
A. G. W. Whitfield

7. The following *Associate Members* were re-elected for a further period of three years (Rule 11):

D. W. Barritt
R. S. Duff
R. W. Emanuel
P. M. McAllen
A. C. MacDonald
H. J. S. Matthew
M. B. Matthews
T. Semple
R. S. Stevens

8. The following new *Associate Members* were elected and introduced to the President and Chairman:

E. F. Chin (Southampton)*
T. B. Counihan (Dublin)
L. G. Davies (London)
D. Emslie-Smith (Dundee)
P. R. Fleming (London)
E. Fletcher (Belfast)
K. Fraser (Glasgow)*
T. Hanley (Epsom)
H. R. S. Harley (Cardiff)*
P. Harris (Birmingham)
P. J. D. Snow (Manchester)
C. Symons (London)
P. Szekely (Newcastle-upon-Tyne)

* Surgical members

9. It was agreed that the following Rules should be altered to read:

Rule 7

. . . . This includes up to 30 Ordinary Members or Associate Members who may be elected for their interest in cardiovascular surgery.

Rule 12

This rule is deleted: see Rule 23

Rule 22 (renumbered 21)

. . . or one of the Editors delegated by him to act as his deputy, the Secretary, and the Treasurer. Two of . . .

Rule 23 (renumbered 22)

. . . . For Ordinary Members it is five pounds and for Associate Members four pounds. This includes the subscription to the British Heart Journal, which is compulsory. Failure to pay . . .

Rule 25 (renumbered 24)

The Council shall nominate two Ordinary Members for election as Secretary and Treasurer; they shall hold office for not more than five years and shall *ex officio* be members of the Council.

Rule 26 (renumbered 25)

The Secretary shall summon all meetings, circulate the programme to members at least one month before the meeting, and be responsible in co-operation with the Chairman Elect for arranging the Annual General Meeting on behalf of the Council. The Secretary shall keep brief minutes of the proceedings of the Society.

Rule 26 (new rule)

The Treasurer shall keep the accounts, collect subscriptions, and be responsible for the expenditure of the Society.

10. John Goodwin was elected *Honorary Treasurer* of the Society.
11. The plans of the National Association for the Prevention of Tuberculosis to change its name to the National Chest and Heart Association and to widen its work to include heart disease were reported. The Association had asked the British Cardiac Society to appoint three representatives to meet them to discuss these future plans, and the Council had appointed the President, Morgan Jones, and Paul Wood to meet them and report back to the Council.
12. The Annual General Meeting to be held at Cardiff on Thursday, April 9, 1959, the day before the Meeting of the Association of Physicians.

DEMONSTRATIONS were held in Littlewood Hall, at the Leeds General Infirmary, during both days.

On the first day lunch was served in the Nurses Recreation Room of the Leeds General Infirmary by invitation of the Board of Governors.

After a sherry party in the Parkinson Building given by the local members, the Society dined together in the University Refectory with John Towers in the Chair. After dinner J. K. Rennie proposed the health of the Chairman and the Chairman replied.

SCIENTIFIC COMMUNICATIONS

THE MECHANISM OF ACUTE HYPOTENSION FROM EMOTION

By E. P. Sharpey-Schafer and C. J. Hayter (*introduced*)

Continuous records of arterial pressure, arterial oxygen saturation, and the resistance of forearm vessels were obtained before and during nitrous oxide anæsthesia for extraction of teeth. Five of twenty-five subjects developed arterial hypotension and vasodilatation in the forearm, showing that the final mechanism was the vaso-vagal fainting reflex. The time of onset of hypotension and the heart rate and pulse pressure of those subjects who did not faint indicated that fear of the dental chair was a major precipitating factor. Since cases of heart failure never show emotional fainting, emptying of the normal heart during systole seems to be the mechanism that fires the afferent part of this reflex.

FACTORS THAT PRECIPITATE MYOCARDIAL INFARCTION

By L. G. Davies and J. D. Hunter (*introduced*)

Myocardial infarction may be precipitated by a variety of conditions, for example unaccustomed exertion, large meals, and alcoholic excess; but in the ordinary run of cases these factors are seldom noted. Eighty men between the ages of 40 and 69 years were interviewed within six weeks of their infarction, and careful enquiry made into possible precipitating factors. It was assumed that the onset of pain indicated the onset of infarction. Three main points emerged.

(1) The onset of infarction was more often within two hours of an ordinary meal than might have been expected by chance.

(2) In one third of the patients infarction occurred during sleep, but the distribution was uneven, with the maximum incidence during and around the third hour.

(3) Infarction occurred more frequently when subjects were travelling to work than when they were travelling home.

These findings recall the behaviour of angina, which is often worse after a meal, is more troublesome in the morning (first effort angina), and, when it occurs at night, is most common during the first four hours of sleep.

Factors that aggravate angina often seem, therefore, to precipitate infarction. A study of these factors might help us to understand why thrombosis occurs in coronary vessels.

Mitral Stenosis with Jet Regurgitation

By A. A. F. Peel

Mitral regurgitation exists in two forms—free regurgitation in which valve cusps are thickened and distorted but there is no narrowing, and jet regurgitation where there is mitral stenosis, often of extreme degree, with thickening and rigidity of the edges of the mitral orifice so that opening and closing of the valve are alike impossible. In some cases of jet regurgitation the signs of stenosis predominate, with a loud systolic murmur as an additional finding; the problem is not one of diagnosis but of treatment—will a valvotomy improve or aggravate the patient's disability? Not infrequently, however, the dominant signs are those of severe regurgitation so that operation is not even contemplated, and the very existence of stenosis may be overlooked; yet dramatic improvement has followed a free valvotomy in such a case.

Two cases are described in detail, the first verified at autopsy and the second at a repeat valvotomy which produced a very good result. Brief particulars, with operative findings and results, in a series of 10 additional cases are quoted. The differential diagnosis between "free" and "jet" regurgitation is discussed, important features being size, degree of filling, and amplitude of pulsation of the left ventricle, presence or absence of pulmonary hypertension, and nature of "wedged catheter" pressure curve.

Ventilatory Cost for Exercise Before and After Mitral Valvotomy

By J. P. P. Stock and M. C. S. Kennedy (*introduced*)

We have previously reported ventilatory findings in mitral stenosis (*Lancet*, 1953, **2**, 5). We now present measurements of the ventilatory cost for exercise before and after operation in 85 patients with mitral stenosis treated surgically and similar data from a further 20 patients whose symptoms did not warrant operation. In 36 patients, we have serial observations over three or more years after operation. Analysis of the data before operation confirms our previous finding that increasing disability in mitral stenosis tends to be associated with an increasing ventilatory cost for exercise. The mean value for the standardized ventilation at 300 kg/metres per minute for clinical grade I patients was 27 litres/minute (S.D. 4·7); for grade II, 35 (S.D. 8·1); for grade III, 44 (S.D. 9·2); rising to 62 litres/minute (S.D.14) for grade IV patients. There is, however, a considerable overlap between the grades. Nevertheless, only three of the 85 patients treated surgically showed a completely normal ventilatory cost for exercise. Ventilatory cost was found to correlate more closely with the pulmonary vascular resistance ($R = 0{\cdot}61$) than with the left atrial pressure or Wood's mitral index.

Following surgery, ventilatory cost fell to normal or near normal levels in 28 of 30 cases classed as a good result clinically. Moreover, the test seemed quickly to reflect re-stenosis, the standardized ventilation often beginning to rise before the reappearance of symptoms.

The Diverse Effects of Ganglion Blocking Agents in Mitral Valve Disease

By J. F. Goodwin, A. Hollman, and T. V. O'Donnell (*introduced*)

The acute effects of hexamethonium upon the circulation have been studied in 32 cases. Pulmonary artery pressure, cardiac output, and (in 14 cases) pulmonary capillary venous pressure have been measured before and after intravenous administration of the drug, and the results have been analysed together with those in 43 cases published by other workers.

The results are presented according to the effect on cardiac output, which fell in one third, rose in one third, and remained unchanged in one third, of the cases in our own series. When the cardiac output fell, the pulmonary arterial pressures fell also. But in about half the total of 75 cases the cardiac output rose or remained unchanged, while the pulmonary arterial pressure fell, suggesting release of pulmonary vasoconstriction.

In 32 cases (9 of our own and 23 reported by others), pulmonary venous pressures were also measured. When the output was unchanged, the pulmonary capillary venous pressure fell in all but one. When the cardiac output rose, the pulmonary capillary venous pressure fell in all but two, and was accompanied by a fall in pulmonary arterial pressure. In three reported cases the pulmonary capillary venous pressure and cardiac output rose while the pulmonary arterial pressure fell, affording evidence for release of pulmonary vasoconstriction.

The possible reasons for these variable effects in mitral disease are discussed. In a small number of cases, the actions of these drugs suggested release of pulmonary vascular tone.

Combined Radner and Brock Techniques for Recording Left Heart Pressures

By W. A. Mackey and R. M. Thomson (*introduced*)

In a small series of cases, puncture of the aorta, main pulmonary artery, or left atrium has been combined with percutaneous puncture of the left ventricle, using the methods of Radner and of Brock and his associates. To measure pressure gradients across the mitral valve, the left atrium was punctured by the suprasternal route, and the left ventricle through the apex. In aortic valve disease, pressures in the aorta and left ventricle were measured simultaneously. Cardiac output was determined by withdrawing blood samples from the main pulmonary artery and the left ventricle simultaneously. The method has proved relatively straightforward, and there have been few complications and these only minor ones.

By this means, left heart pressures can be recorded quickly and reliably without the tedious procedures involved in right or left heart catheterization. The technique is briefly described and its advantages and disadvantages discussed.

Demonstrations

Stellate Ganglion Block in Angina Pectoris

By J. J. Ablett and P. G. F. Nixon (*introduced by John Towers*)

Patients greatly disabled by long-standing and relatively stable angina pectoris have been subjected to stellate ganglion block. Contrast medium has shown downward spread of local anæsthetic to the level of the fourth and fifth dorsal ganglia. In some patients the manœuvre has abolished pain, and made possible a greatly increased amount of effort before the onset of anginal pain and the appearance of ischæmic S–T depression. The increased exertion, often strenuous, has not caused apparent harm. Surgical sympathectomy has benefited these patients. It has not been offered to patients whose symptoms were unrelieved by stellate ganglion block.

The fact that stellate ganglion block may greatly increase the amount of effort required to produce ischæmic S–T depression suggests that in some subjects it acts by increasing myocardial blood supply as well as by blocking pain pathways.

Total Right Pulmonary Venous Drainage into the I.V.C., with Intact Atrial Septum: Surgical Correction by Transfer to Left Atrium

By J. A. Aylwin and P. G. F. Nixon (*introduced*)

A left-to-right shunt similar in many respects to that of atrial septal defect occurs when an anomalous vein directs the entire pulmonary flow from one lung into the inferior vena cava above the diaphragm. The defect occurs so rarely as an isolated abnormality that the important clinical features, found before surgical correction in a woman aged 47 years, are recorded.

A parasternal heave of right ventricular over-activity, and a pulmonary systolic ejection murmur were present, as in atrial septal defect. There were, however, three points of difference. In expiration aortic and pulmonary valvular closure occurred simultaneously. During inspiration the pulmonary second sound split normally. The electrocardiogram showed a dominant R in V3R, but no bundle-branch block pattern. At cardiac catheterization pulmonary arterial systolic pressure was 30 mm. Hg.

Variations in the Atrial Sound

By John Barlow and Priscilla Kincaid-Smith (*introduced by J. P. Shillingford*)

Clinical and phonocardiographic observations on the atrial sound in hypertension, ischæmic heart disease, cor pulmonale, and other conditions have shown that it is subject to variation in certain circumstances. With improvement in cardiac status, the atrial sound approaches the first heart sound (Duchosal 1933, 1935). In some cases it remains as an atrial component of the first heart sound. Certain procedures can alter the timing of the atrial sound in hypertension. Hypotensive drugs cause the atrial vibration to move towards the first heart sound and finally to disappear altogether. If postural hypotension is induced in the sitting position, the sound vibration reappears on lying down as the blood pressure rises. "Venesection" by cuffs produces a similar but smaller effect. Amyl nitrite inhalation invariably causes a movement of the atrial sound towards the first sound in hypertension but we have not demonstrated a similar change in ischæmic heart disease, cor pulmonale, or when the atrial sound is due to a prolongation of the P–R interval. In cor pulmonale the atrial sound moves away from the first sound on inspiration and towards it on expiration; there may be an accompanying change in amplitude.

Carotid sinus pressure usually produces a diminution in amplitude of the atrial sound and where the P–R interval is prolonged by this manœuvre the atrial sound moves in the same direction and to the same extent as the P wave.

Tomography of Calcified Aortic and Mitral Valves

By Paget Davies and N. L. Bucky (*introduced by S. Oram*)

The history and significance of calcified aortic and mitral valves was briefly reviewed. The clinical features and radiological findings of twenty patients with aortic valve calcification and fifteen with mitral valve calcification were recorded.

The influence of mitral calcification on the mitral rhythm of Duroziez, incompetence of the valve, and valvotomy was discussed. The rarity of mitral valve calcification in association with calcific aortic stenosis was noted: it occurred in only 2 out of a series of 35 patients.

While admitting that fluoroscopy is essential, we think that tomography of the heart valves is of considerable value. Not only does it give a permanent record of valve calcification but it may detect such calcification when fluoroscopy has failed to do so. Tomography will show which valve is affected from the form and position of the calcification.

The Value of Serum Transaminase Levels in the Diagnosis of Myocardial Infarction

By P. R. Fleming and J. Pryse-Davies (*introduced by R. I. S. Bayliss*)

The serum glutamic-oxalacetic transaminase has been estimated in 50 patients in whom myocardial infarction was suspected. In confirmation of previous work, it was found that peak values were reached 12–24 hours after infarction, the level falling to normal in 5–7 days.

In all cases in which the diagnosis was confirmed by unequivocal electrocardiographic changes or by autopsy, diagnostic elevation of the serum transaminase level was found, provided that samples were obtained sufficiently close to the time of infarction. Serial sampling increased the chances of a positive diagnosis. In some cases elevation of the transaminase level was the earliest definite evidence of infarction. There appeared to be some relation between the peak value reached and the prognosis, confirming previous work in dogs on the relation between the level of serum transaminase and the size of experimental infarcts.

False positive results were seen in two patients with lesions of the liver and pancreas, but not in cases of severe angina without infarction.

The Speed of Pulmonary Blood Flow in Atrial Septal Defect

By L. McDonald, R. Emanuel, and M. Towers (*introduced*)

The pulmonary blood flow is known to be increased in uncomplicated atrial septal defect, due to the left-to-right shunt. The increased flow (measured in volume per unit of time, i.e. litres a minute) may reflect an increase in the circulating pulmonary blood volume or in the speed of flow or in both. In relation to these problems patients with atrial septal defect were compared with others who did not have intracardiac shunts.

The speed of pulmonary blood flow was studied by a dye-dilution technique during right-heart catheterization. T. 1824 was injected at various sites in the heart and great vessels, and the initial passage of dye was recorded by an ear densitometer. The time from the injection of dye to its appearance at the ear was measured on the dye-dilution curves obtained. The appearance times after injection into the pulmonary artery were found to be significantly shorter in patients with atrial septal defect. A return to normal has been demonstrated after closure of the septal defect. These findings indicate an increased speed of pulmonary blood flow in atrial septal defect; and their importance is discussed in relation to other clinical and hæmodynamic features of the condition.

Mobile T Wave Inversion in Chest Leads

By P. G. F. Nixon (*introduced*)

Electrocardiograms from nine subjects with a common abnormality were presented. One or more chest leads showed an inversion of the T wave that was greater in V3 or V4 than in V1 or V5. The inversion was termed mobile because it readily disappeared during or after Valsalva's manœuvre, the waves becoming upright and normal in shape and size.

In six of the nine, the mobile inversion was regarded as innocent, because no disease likely to be responsible could be found and because the subjects were capable of exerting themselves to exhaustion without angina pectoris, S–T segment depression, or an abnormal degree of breathlessness. After exercise the T waves became normal for a short period.

Two patients had long-standing angina pectoris. The standard limb and aV leads were normal, but mobile inversion of T in V3 and V4 was usually present at rest: after exercise this became normal, and no ischæmic S–T depression appeared. The ninth patient complained of fatigue and slight shortness of breath, and had a remarkably mobile inversion of T in V3 and V4, other leads being normal; and gentle exercise caused pathological depression of the S–T segment: subsequently he developed angina pectoris, and the mobile T wave inversion was attributed to acute coronary insufficiency.

In ten consecutive cases of acute anterior cardiac infarction tested with Valsalva's manœuvre, the inverted præcordial T waves did not become upright, and their inversion was termed immobile. In some cases the replacement of an inverted by a normal T may be due to movement of the affected part of the heart away from the electrode. In others this explanation is hardly acceptable because the T wave recovery that can be obtained by Valsalva's manœuvre, hyperventilation, or exercise appears to be independent of respiratory movement and posture.

Hæmolysis in the Extracorporeal Circulation

By P. G. F. Nixon (*introduced*)

Blood damage in the extracorporeal circulation was studied experimentally with the Leeds modified Melrose—N.E.P. heart-lung machine. Hæmolysis was measured by changes in the plasma hæmoglobin level. Ox blood was used because it appeared to resemble human blood in its response to mechanical injury. Pig blood was found to have too high a resistance to mechanical injury.

High rates of pumping and fast rates of rotation of the oxygenating cylinder caused little hæmolysis. The introduction into the circuit of high resistance to flow in the form of a filter chamber caused gross hæmolysis. After redesigning the filter chamber to eliminate constrictions and sharp bends its resistance was greatly lowered and significant hæmolysis no longer occurred.

The Effect of Reduction in Venous Return to the Heart on the Left Atrial Pressure Curve

By P. G. F. Nixon (*introduced*)

After recording the resting left atrial pressure pulse in patients with mitral disease by the method of Allison and Linden, venous tourniquets have been applied to the thighs. Within as short a period as five minutes changes have occurred in the pulse wave; the mean pressure (M) has fallen, the height of V has fallen by a disproportionately greater amount, and the values for V/M and Ry/V have become smaller.

In dogs with normal mitral valves, the author has shown that the left atrial V wave disappears almost completely after occlusion of the inferior vena cava for one minute.

If the upstroke of the V wave represents the rise in pressure that is caused by blood flowing into the atrium during the period of mitral valve closure, and if the atrium does not rapidly alter its volume elasticity characteristics with changes in the amount of blood filling it, it follows that the V wave will become smaller when the inflow is reduced.

It is suggested that the character of the V wave may be a misleading index to mitral valve function if the cardiac output is not considered.

Changes in the Electrocardiographic Pattern of Right Ventricular Hypertrophy Following Mitral Valvotomy

By R. R. Torres (*introduced*), J. Mackinnon, D. E. Anderson (*introduced*), and E. G. Wade

Electrocardiographic signs of right ventricular hypertrophy (RVH) are good indirect evidence of a high pulmonary vascular resistance (PVR) and their disappearance after mitral valvotomy indicates a fall in PVR and pulmonary arterial pressure. Sixty patients with mitral stenosis and electrocardiographic evidence of RVH (Criteria: Milnor, W. R. (1957), *Circulation*, **16**, 348) were submitted to valvotomy between 1952 and 1957. The 48 survivors have been closely followed and these changes were related to functional improvement and the valve size before and after operation.

The electrocardiogram reverted to normal in 27 (56%), improved in 8 (17%), and was unchanged in 13 (27%). The proportion where the valve was well split was approximately the same in all groups. The time required for this reversion to normal ranged from less than three months to two years. There was a close but not complete correlation between these changes and functional improvement.

It is concluded that in approximately one half of the cases with very high PVR, pressures may ultimately return towards normal but there appears to be no way of distinguishing them. Good splitting of the valve is a pre-requisite but in about a quarter the high pulmonary artery pressure and PVR are apparently irreversible.

After the demonstrations there was a

Symposium on the Extra-Corporeal Circulation

This was opened by Professor A. Hemingway of Leeds. Professor A. C. Brom of Leiden, Dr. L. Radigan of Indianapolis, and Mr. G. H. Wooler and Dr. P. G. F. Nixon of Leeds were other invited speakers.

SECOND DAY. SHORT COMMUNICATIONS

The first three communications were given before the Symposium on Diuretics in the morning, and the remainder at the afternoon session.

The Lymphatic Drainage of the Heart

By P. R. Allison

A short historical account of the previous investigations into the lymphatic drainage of the heart was presented. Experiments have been carried out to inject the sub-epicardial lymphatics of the heart and the main gland stations in the mediastinum have been noted. This work has been done mainly on dogs. Particulate matter has also been injected into the pericardial sac and its absorption into the lymphatic system charted.

Polythelia in Cardio-arterial Disease

By William Evans

Polythelia, the presence of accessory nipples, was sought in 2000 consecutive patients attending for examination of the heart. Since polythelia is a manifestation of atavism, its association with any particular disease suggests that this has a congenital basis. Its frequency in systemic hypertension, pulmonary hypertension, and myocardial fibrosis favours a congenital predisposition for these three clinical states.

The Cause of a High Jugular Venous Pressure in Certain Cases of Atrial Septal Defect

By Paul Wood

The jugular venous pressure was raised conspicuously in 23 of a consecutive series of 300 cases of atrial septal defect with left-to-right shunt. A left-sided lesion, such as mitral stenosis or essential hypertension, helped to explain the hæmodynamics in 16; but in 7 instances there was no evidence of a left-sided lesion, and in the only one that came to necropsy the left ventricle was normal but small.

An analysis of these seven cases revealed an average pulmonary/systemic flow ratio of 3·5, which was about the same as in the rest of the series (3·6). They differed chiefly from those with normal venous pressure in that their average age was 51 (22 in the rest of the series); six of them had atrial fibrillation (1% in the rest of the series), and they all seemed to have tricuspid regurgitation.

Differential manometric studies showed that the chief left-to-right pressure gradient across the defect occurred during ventricular systole in all simple cases of atrial septal defect, but in two out of three cases with atrial fibrillation it was during ventricular diastole.

It is suggested, therefore, that atrial fibrillation in atrial septal defect encourages tricuspid regurgitation, and that this abolishes or reduces the systolic pressure gradient, the maximum shunt then taking place in diastole. The large pulmonary blood flow that has been demonstrated in these cases builds up a high systolic pressure in the left atrium when outflow to the right atrium is impeded, and prevents reversal of the shunt; instead both left atrial and jugular venous pressures rise, at any rate during ventricular systole. Only when the volume of blood entering the left atrium from the lungs is sufficiently diminished can the shunt be reversed. The chief agents complicating cases of atrial septal defect that may be responsible for such an effect are a raised pulmonary vascular resistance and partial anomalous pulmonary venous drainage into the right atrium.

The Nature and Prognosis of Thyrotoxic Heart Disease Treated with ^{131}Iodine

By G. Sandler (*introduced by G. M. Wilson*)

Evidence of heart disease was present in 150 out of 462 thyrotoxic patients treated with ^{131}I. These patients were mainly in the older age groups and many were gravely ill as a result of cardiac complications. This treatment carried a negligible mortality, produced a permanent cure of the hyperthyroidism, and afforded an opportunity to study the subsequent course of the heart disease.

In 85 patients there was associated heart disease—ischæmic, hypertensive, rheumatic, pulmonary, or congenital in origin. In 65 patients there was auricular fibrillation, congestive failure, or cardiomegaly in the absence of clinical, radiological, or electrocardiographic evidence of associated heart disease. The nature of the underlying lesion in the latter patients is discussed in the light of the changes observed after treatment of the thyrotoxicosis and the autopsy findings in five cases. The prognosis of auricular fibrillation, congestive failure, and cardiomegaly is described in relation to the age, sex, severity of the thyrotoxicosis, and nature of the associated heart disease.

Sympathectomy for Hypertension. Long-term Follow-up

By C. P. Newcombe (*introduced by J. R. H. Towers*)

212 patients, who had sympathectomy performed by Mr. H. S. Shucksmith for hypertension, were observed for periods of three to nine years. The classification described by Palmer, Loofbourow, and Doering (1948: *N. Eng. J. Med.*, **239**, 990) was used. In groups 1, 2, 3, and 4 containing 55, 50, 77, and 30 patients the mortality was respectively 4, 16, 36, and 83 per cent.

Improvement in the retinopathy was not seen in those cases of malignant hypertension who died within eighteen months of operation, whereas improvement occurred in eight of the nine cases who lived two years or more after operation, and in six papillœdema, hæmorrhages, and exudates regressed completely. Of those who had retinitis without papillœdema the exudates and hæmorrhages absorbed in twenty-two out of thirty-one, eighteen of these being still alive, whereas only one of the nine who failed to improve is still living.

In a quarter of the living cases there has been a sustained reduction of diastolic pressure of over 15 mm. In half the patients headache, and in a third dizziness were completely relieved, and in the remainder they were substantially diminished.

The Diagnosis of Left Ventricular Hypertrophy

By G. W. Hayward and David Weitzman

One hundred patients with some evidence of left ventricular hypertrophy were studied in order to assess the reliability of palpation, radiological appearance, and electrocardiography in early diagnosis.

Palpation is influenced by obesity and by emphysema. With the anterior X-ray, there may be disagreement in all except those with much enlargement. In the left oblique view, overlapping of the spine is usual, only when there is obvious enlargement in the anterior view. There is good correlation between the electrocardiogram and other evidence in cases showing tall R waves and ST–T changes, but not when there are tall R waves only or when ST–T changes are due to ischæmia.

Three Cases of Pulseless Disease

By M. H. Lessof (*introduced by C. G. Baker*)

Two cases of large vessel arteritis are reported, together with the necropsy findings in a third case (originally described by Lewis and Stokes in 1942). In both cases studied clinically there was evidence of a diminished blood flow in the legs as well as in the arms. In one, lupus erythematosus cells were repeatedly found in the blood despite an absence of the common clinical features of this condition. The histological appearances of the arteries in pulseless disease are illustrated. (*To be reported.*)

Endocardial Fibro-elastosis (Infantile Type)

By R. I. K. Elliott (*introduced by R. Kemball Price*)

Endocardial fibro-elastosis is a finding common to several distinct and separate conditions. In this country, two types, fœtal and infantile, are recognized. In the fœtal type death occurs in the first few days of life; aortic hypoplasia or atresia and an inactive left ventricle are present, together with sclerema (Ballantyne's pre-agonal induration).

In the infantile type death occurs between six months and six years, in children previously fit, after a short illness, usually lasting only a few hours. The heart is three to five times normal size: apart from the size and the fibro-elastosis it is anatomically normal. The clinical and pathological features of three cases of this type are presented.

It is concluded that whereas the fœtal type of fibro-elastosis is a developmental defect not intrinsically different from other types of congenital heart disease, the infantile type is a form of cardiomyopathy (Brigden, 1957). The two conditions, in fact, have nothing but the endocardial thickening in common, so that the nomenclature might with advantage be revised. The nature of the defect in the cardiac muscle in this type of fibro-elastosis is obscure, but it is by no means rare, and was the cause of death in 1·3 per cent of all live-born infants and children up to ten years old coming to necropsy in the Brighton area in the last five years.

Valsalva's Manœuvre and Oximetry in Atrial Septal Defect

By M. B. McIlroy (*introduced by P. Wood*)

The effect of Valsalva's manœuvre on the arterial pressure and arterial oxygen saturation has been measured in 75 patients with atrial septal defect. As has been shown by Lee and Gimlette, shunt reversal after Valsalva's manœuvre results in a drop in arterial oxygen saturation which can be measured with an ear oximeter.

In patients with small or moderate shunts through an atrial septal defect, the left-to-right shunt reverses temporarily after Valsalva's manœuvre. In patients with large shunts, the arterial pressure response to Valsalva's manœuvre is square wave in type and shunt reversal does not occur. These results confirm the usefulness of the simple oximetric test for atrial septal defect described by Lee and Gimlette and also indicate that the arterial response to Valsalva's manœuvre in patients with atrial septal defect can be used as a measure of the size of the shunt.

The Assessment of Mitral Stenosis and Regurgitation by Left Heart Catheterization

By E. W. Hancock (*introduced by C. G. Baker*)

Clinical assessment of the degree of mitral stenosis or of the relative importance of mitral stenosis and regurgitation still presents difficulties in particular cases. Left atrial catheterization by the Bjork method has been carried out in 60 patients with mitral valve disease, and the results subsequently correlated with operative or post-mortem findings in 45 of them. The accuracy of predictions of valve size in pure mitral stenosis

has been confirmed. The assessment of valve size in the presence of regurgitation was discussed, including the value of the left atrial pulse form, and of dye dilution curves in the assessment of regurgitation. The distinction between pure mitral regurgitation and mixtures of mitral stenosis and regurgitation was described and correlated with clinical features.

Coronary Artery Catheterization, with Pressure Records, during Thoracic Aortography

By A. M. Johnson (*introduced by C. G. Baker*)

Reported in full: *Brit. Heart. J.*, **20**, 411, 1958.

SYMPOSIUM ON DIURETICS

The Treatment of Œdema in Congestive Heart Failure

By O. Brenner

Low sodium diets are of great value in the treatment of congestive failure, but since normal kidneys conserve salt, excretion of sodium soon falls to or below the intake; and, unless cardiac function improves or diuretics are given, there will be no loss of the sodium and water already accumulated. There may instead be retention of water without sodium, resulting in dilution hyponatræmia.

Mercurial diuretics can usually, if necessary, be given safely for years, but in resistant cases, uræmia may occur suddenly with a rise in blood urea sometimes to over 300 mg. per 100 ml. in a few days. Recovery often occurs if the mercurial diuretic is stopped. It should not be given unless the blood urea the day before is less than 70 mg. per 100 ml. In resistant cases, diuresis can be restored or increased by a slow intravenous injection of 0·5 g. aminophylline two hours after each mercurial injection.

In severe heart failure, the serum sodium and chloride concentrations tend to be low and the serum potassium high. This is not due to too drastic salt restriction or excessive use of mercurial diuretics, since similar changes occur in patients taking a normal diet, and receiving no mercurial diuretics. It is due to anoxic damage to cells, allowing potassium to escape from them into the plasma, to be excreted in the urine, so that potassium depletion occurs despite a raised serum potassium concentration, while sodium and chloride leave the plasma to enter the cells, so that their serum concentration falls while the total body sodium and chloride content may rise. Attempts to force the cells to retain potassium by giving supplements of potassium together with glucose and insulin may promptly be followed by diuresis and loss of œdema in patients previously unresponsive to treatment.

Diamox, Mictine, and Rolicton

By T. Hanley

The properties of three oral diuretics were discussed.

Amino-metradine (*mictine*). This earlier compound given in a dosage of 400–800 mg. daily promotes a diuresis which at its peak is roughly half that given by 2 ml. of mersalyl intramuscularly. The net diuresis of amino-metradine given for several days may be comparable with that of 2 ml. mersalyl on alternate days (Platts and Hanley, 1956, *Lancet*, **1**, 357). Amino-metradine tends to cause nausea and vomiting.

Amiso-metradine (*rolicton*). This improved closely-related compound has superseded mictine. It has similar effects on urine electrolytes, increasing the excretion of sodium and chloride ions, but 1600–2400 mg. daily are required for an equivalent diuresis. In such dosage side-effects are trivial (Platts, personal communication). The drug is best reserved for the treatment of mild heart failure or prophylaxis of œdema and is not suitable as the sole diuretic in severe heart failure.

Acetazolamide (*diamox*). In a dose of 250–500 mg. daily acetazol-amide causes a maximum diuresis approximately equal to 1 ml. of mersalyl intramuscularly, but repeated administration very rapidly leads to "resistance" to the drug. Acetazol-amide acts by increasing urinary bicarbonate excretion; it causes a metabolic acidosis and this brings into play renal homeostatic mechanisms which limit further bicarbonate loss. This resistance cannot be overcome by increasing the dose, and natural recovery from the acidosis requires at least three days. Acetazol-amide should, therefore, be given at intervals not shorter than three days and its intrinsic diuretic effect is consequently small. It may have a place in correcting the metabolic alkalosis sometimes associated with mercurial resistance.

Chlorothiazide. Renal Mechanisms in Diuresis

By M. D. Milne (*introduced*)

Chlorothiazide is the most potent oral diuretic introduced up to the present. Since it contains a free $-SO_2.NH_2$ group, chlorothiazide is a carbonic anhydrase inhibitor both *in vitro* and *in vivo*. Like acetazolamide, it alkalinizes the urine and increases potassium and bicarbonate excretion, but chlorothiazide, in addition, greatly diminishes the tubular reabsorption of chloride, with consequent increased output both of sodium and chloride.

In assessing the effectiveness of any diuretic, loss of sodium is highly desirable, while loss of potassium is undesirable and often actually harmful. In general, potassium loss increases with rise of urinary pH and with the severity of the heart failure that is being treated. In severe resistant heart failure there is secondary hyperaldosteronism which enhances tubular exchange of potassium for sodium. Chlorothiazide causes greater loss of potassium than mercurial diuretics, but less than the more powerful carbonic anhydrase inhibitor, acetazolamide. Unlike mercurial diuretics, the efficacy of chlorothiazide is not reduced by hypochloræmic alkalosis. Ammonium chloride therapy is therefore unnecessary, but potassium chloride should always be given to prevent potassium deficiency. The action of chlorothiazide and mercurials is additive, and therefore, in refractory cases of cardiac œdema, they can be prescribed together.

Chlorothiazide is distributed solely within the extracellular space, and does not appreciably enter the body cells. It is very rapidly excreted in the urine, the clearance being higher than the glomerular filtration rate. Although it does not appear to be metabolized in the body, recoveries of the drug in urine are lower after an oral dose than after an intravenous injection. An average of only 30 per cent is absorbed from the gut, but this is sufficient to produce a satisfactory diuretic response. Like other carbonic anhydrase inhibitors, chlorothiazide reduces urinary citrate and therefore tends to the precipitation of calcium phosphate in urine. Renal calculus formation has complicated long periods of acetazolamide therapy, but it is not yet known whether this will occur after prolonged use of chlorothiazide.

Electrolyte Metabolism in Oedema and Diuresis

By D. A. K. Black (*introduced*)

The importance of the "low-salt syndrome" and of potassium depletion in heart failure are discussed. The term "low-salt syndrome" is not, in my view, a happy one, for a low plasma sodium can be brought about by several quite different mechanisms, and a good response to hypertonic saline, as advocated by Schroeder in the original description, is rarely seen. A blood urea level over 100 mg. per 100 ml., in the absence of renal disease, can be a useful indication for an attempt to improve the renal circulation by a small amount (200 ml.) of 5 per cent saline; this can be repeated if the blood urea falls appreciably, but not otherwise.

Potassium depletion in cardiac failure can be caused by anorexia, by urinary losses during diuresis on a low-sodium diet, by the use of resins, or by the action of aldosterone on the kidneys. Conventional indices of potassium depletion are often normal, but increasing sensitivity to digitalis may occur as potassium depletion develops. Oral potassium supplements may be of value in patients who have become resistant to diuretic agents.

INDEX OF AUTHORS

A

Abdin, Zahira, H.: Electrocardiogram in aortic stenosis. 31.
Amoroso, E. C. (and G. S. Dawes and Joan C. Mott): Patency of the ductus arteriosus in the newborn calf and foal. 92.
Angelino, P. F. (and R. Garbagni, A. Brusca, and E. Minetto): Residual lung volume in mitral disease. 479.
Ansell, B. M. (and E. G. L. Bywaters, and I. Doniach): Aortic lesion of ankylosing spondylitis. 507.
Apthorp, G. H. (and M. B. McIlroy): Pulmonary function in pulmonary hypertension. 397.

B

Barlow, J. (and J. Shillingford): The use of amyl nitrite in differentiating mitral and aortic systolic murmurs. 162.
Belcher, J. R.: Restenosis of the mitral valve. 76.
Besterman, E. M. M.: Effects of acute cardiac infarction and of heparin therapy on the lipoproteins. 21.
Boyd, J. F. (and S. D. Scott Park, and George Smith): Correlation between various assessments of pulmonary arterial pressure in mitral stenosis. 466.
Brennan, C. F. (and Evan Fletcher): Digitalis and intractable heart failure. 204.
Briggs, R. M. (and J. Mackinnon): Patent ductus arteriosus with mitral stenosis. 424.
Brotmacher, L. (and Maurice Campbell): The natural history of ventricular septal defect. 97.
—— (and Maurice Campbell): Ventricular septal defect with pulmonary stenosis. 379.
Bruns, D. L. (and L. G. Van der Hauwaert): Aortic systolic murmurs developing with increasing age. 370.
Brusca, A. (and R. Garbagni, P. F. Angelino, and E. Minetto): Residual lung volume in mitral disease. 479.
Burry, A. F.: Supra-aortic stenosis associated with Marfan's syndrome. 143.
Bywaters, E. G. L. (and B. M. Ansell, and I. Doniach): Aortic lesion of ankylosing spondylitis. 507.

C

Campbell, Maurice (and L. Brotmacher): The natural history of ventricular septal defect. 97.
——: Unilateral rib-notching from the collateral circulation after division of the subclavian artery. 253.
—— (and L. Brotmacher): Ventricular septal defect with pulmonary stenosis. 379.
Cardus, D. (and J. Mackinnon, and G. Wade): Circulatory effects of changing position in mitral disease. 233.
Chamberlain, E. N. (and C. A. St. Hill, and S. Cope): Anti-streptolysin O titre in rheumatic carditis. 183.
Chesler, E.: Serum glutamic oxalacetic transaminase levels in diphtheritic myocarditis. 244.
Clare, F. B. (and R. Gorlin, and J. J. Zuska): Evidence for pulmonary vasoconstriction in man. 346.
Collins, D. M. (and T. East, M. P. Godfrey, P. Harris, and S. Oram): Ventricular septal defect with pulmonary stenosis and aortic regurgitation. 363.
Cope, S. (and E. N. Chamberlain, and C. A. St. Hill): Anti-streptolysin O titre in rheumatic carditis. 183.
Coulshed, N. (and E. Wyn Jones): Tracheal vascular ring causing dyspnœa. 147.
——: Incompetent congenital bicuspid right atrio-ventricular valve. 433.
Cropp, G. J. (and G. W. Manning): Electrocardiogram in progressive muscular dystrophy. 416.
Cutforth, R. H. (and S. Oram): Electrocardiogram in pulmonary embolism. 31.

D

Davidson, L. A. G. (and H. A. Dewar): Cerebral blood flow in mitral stenosis and its response to carbon dioxide. 516.
Davies, L. G.: Observer variation in reports on electrocardiograms. 153.
Dawes, G. S. (and E. C. Amoroso, and Joan C. Mott): Patency of the ductus arteriosus in the newborn calf and foal. 92.
Dewar, H. A. (and L. A. G. Davidson): Cerebral blood flow in mitral stenosis and its response to carbon dioxide. 516.
Doniach, I. (and B. M. Ansell, and E. G. L. Bywaters): Aortic lesion of ankylosing spondylitis. 507.

E

East, T. (and D. M. Collins, M. P. Godfrey, P. Harris, and S. Oram): Ventricular septal defect with pulmonary stenosis and aortic regurgitation. 363.
Emslie-Smith, D.: The spatial vectorcardiogram in hypothermia. 175.
Evans, William (and D. S. Short): Pulmonary hypertension in congenital heart disease. 529.

F

Fabricius, J. (and W. Falholt): Evaluation of dye injection methods in congenital heart disease. 117.
Falholt, W. (and J. Fabricius): Evaluation of dye injection methods in congenital heart disease. 117.
Fischmann, E. J.: The orthogonal electrocardiogram in left ventricular hypertrophy. 167.
Fletcher, Evan (and C. F. Brennan): Digitalis and intractable heart failure. 204.
French, G.: Aconitine-induced cardiac arrhythmia. 140.

G

Garbagni, R. (and P. F. Angelino, A. Brusca, and E. Minetto): Residual lung volume in mitral disease. 479.
Godfrey, M. P. (and D. M. Collins, T. East, P. Harris, and S. Oram): Ventricular septal defect with pulmonary stenosis and aortic regurgitation. 363.
Gonda, Endre (and János P. Radó, and Erwin Kovács): The role of venous constriction in circulatory disorders. 389.
Goodwin, J. F.: The influence of ventricular hypertrophy upon the cardiogram of anterior cardiac infarction. 191.
Gorlin, R. (and F. B. Clare, and J. J. Zuska): Evidence for pulmonary vasoconstriction in man. 346.
Gunton, R. W. (and C. R. Woolf, and W. Paul): Diagnostic use of an ear oximeter in congenital heart disease. 311.

H

Hamer, N. A. J.: The vectorcardiogram in atrial septal defect. 215.
Harris, P. (and D. M. Collins, T. East, M. P. Godfrey, and S. Oram): Ventricular septal defect with pulmonary stenosis and aortic regurgitation. 363.
Higgins, G. L.: Patent ductus arteriosus with ventricular septal defect. 421.
Hill, Ian (and Hamish Watson, C. Pickard, and K. G. Lowe): Selective cine-angiocardiography with image intensification. 459.
Hollman, A.: Electrocardiographic diagnosis of right ventricular hypertrophy in infancy and childhood. 129.
Hume, Robert: Fibrinolysis in myocardial infarction. 15.

J

James, W. R. L. (and A. J. Thomas): The right ventricle and the small pulmonary arteries in coalworkers. 403.
Johnson, A. M. (and W. D. Logan): Coronary artery catheterization during thoracic aortography. 411.
Jones, E. Wyn (and N. Coulshed): Tracheal vascular ring causing dyspnœa. 147.

K

Kesson, C. W.: Fœtal paroxysmal auricular tachycardia. 552.
Kovács, Erwin (and János P. Radó, and Endre Gonda): The role of venous constriction in circulatory disorders. 389.

L

Leonard, J. J. (and A. M. Weissler, and J. V. Warren): Modification of ventricular gallop rhythm induced by pooling of blood in the extremities. 502.
Linko, Eino (and Erkki Sysimetsa): Clinical and radiological aspects of calcification of the mitral region. 329.
Logan, W. D. (and A. M. Johnson): Coronary artery catheterization during thoracic aortography. 411.
Lowe, K. G. (and Hamish Watson, C. Pickard, and Ian Hill): Selective cine-angiocardiography with image intensification. 459.

M

Mackinnon, J. (and D. Cardus, and G. Wade): Circulatory effects of changing position in mitral disease. 233.
—— (and R. M. Briggs): Patent ductus arteriosus with mitral stenosis. 424.
Manning, G. W. (and G. J. Cropp): Electrocardiogram in progressive muscular dystrophy. 416.
Marques, Mario Gomes: Atrial dissociation. 335.
Martins de Oliveira, Jorge (and Mohinder P. Sambhi, and Henry Zimmerman): Electrocardiogram in pectus excavatum. 495.
McCampbell, S. R.: Direct left atrial pressure tracings and the degree of mitral obstruction. 341.
McIlroy, M. B. (and G. H. Apthorp): Pulmonary function in pulmonary hypertension. 397.
Minetto, E. (and R. Garbagni, P. F. Angelino, and A. Brusca): Residual lung volume in mitral disease. 479.
Misra, S. N. (and L. M. Sanghvi): Electrocardiograms with short P–R interval and aberrant QRS complex. 357.
Mott, Joan C. (and E. C. Amoroso, and G. S. Dawes): Patency of the ductus arteriosus in the newborn calf and foal. 92.
Moulton, R. (and H. G. Spencer and D. A. Willoughby): Noradrenaline sensitivity in hypertension measured with a radioactive sodium technique. 224.
Mounsey, Patrick (and Catherine Neill): Auscultation in patent ductus arteriosus: with a description of two fistulæ simulating patent ductus. 61.
Muller, O. (and K. Rørvik): Hæmodynamic consequences of coronary heart disease. 302.

N

Neill, Catherine (and Patrick Mounsey): Auscultation in patent ductus arteriosus: with a description of two fistulæ simulating patent ductus. 61.
Newcombe, C. P. (and J. R. H. Towers): Myxoma of the left auricle with direct pressure tracings. 575.
Nicks, Rowan: Surgical study of coarctation of the aorta. 351.

O

Oliveira, Jorge Martins de (Mohinder P. Sambhi, and Henry Zimmerman): Electrocardiogram in pectus excavatum. 495.
Oram, S. (and R. H. Cutforth): Electrocardiogram in pulmonary embolism. 31.
—— (and D. M. Collins, T. East, M. P. Godfrey, and P. Harris): Ventricular septal defect with pulmonary stenosis and aortic regurgitation. 363.

P

Papp, Corneilo: Cardiac syncope in atrial septal defect. 9.
Pappas, M. P.: Disappearance of pathological Q waves after cardiac infarction. 123.
Park, S. D. Scott (and J. F. Boyd, and George Smith): Correlation between various assessments of pulmonary arterial pressure in mitral stenosis. 466.
Parkes, W. E.: Thoracolumbar sympathectomy in hypertension. 249.
Paul, W. (and C. R. Woolf, and R. W. Gunton): Diagnostic use of an ear oximeter in congenital heart disease. 311.
Pickard, C. (and Hamish Watson, K. G. Lowe, and Ian Hill): Selective cine-angiocardiography with image intensification. 459.

R

Radó, János P. (and Endre Gonda and Erwin Kovács): The role of venous constriction in circulatory disorders. 389.
Robinson, G. L.: Double-barrelled aorta with bacterial endarteritic vegetations. 571.
Rørvik, K. (and Muller, O.): Hæmodynamic consequences of coronary heart disease. 302.

S

St. Hill, C. A. (and E. N. Chamberlain, and S. Cope): Anti-streptolysin O titre in rheumatic carditis. 183.
Sambhi, Mohinder P. (and Jorge Martins de Oliveira, and Henry Zimmerman): Electrocardiogram in pectus excavatum. 495.
Sanghvi, L. M. (and S. N. Misra): Electrocardiograms with short P–R interval and aberrant QRS complex. 357.
Shillingford, J. (and J. Barlow): The use of amyl nitrite in differentiating mitral and aortic systolic murmurs. 162.
——: Simple method for estimating mitral regurgitation by dye dilution curves. 229.
Short, D. S. (and William Evans): Pulmonary hypertension in congenital heart disease. 529.
Smith, George (and J. F. Boyd, and S. D. Scott Park): Correlation between various assessments of pulmonary arterial pressure in mitral stenosis. 466.
Spencer, H. G. (and R. Moulton, and D. A. Willoughby): Noradrenaline sensitivity in hypertension measured with a radioactive sodium technique. 224.
Storey, Geoffrey: The electrocardiogram in syphilitic heart disease. 483.
Sysimetsa, Erkki (and Eino Linko): Clinical and radiological aspects of calcification of the mitral region. 329.

T

Teare, Donald: Asymetrical hypertrophy of the heart in young adults. 1.
Thomas, A. J.: Coronary heart disease in the presence of pulmonary disease. 83.
—— (and W. R. L. James): The right ventricle and the small pulmonary arteries in coalworkers. 403.
Towers, J. R. H. (and C. P. Newcombe): Myxoma of the left auricle with direct pressure tracings. 575.

V

Van der Hauwaert, L. G.: Aortic systolic murmur developing with increasing age. 370.
Van der Spuy, J. C.: The functional and clinical anatomy of the mitral valve. 471.

W

Wade, G. (and D. Cardus, and J. Mackinnon): Circulatory effects of changing position in mitral disease. 233.
Walmsley, Robert: The orientation of the heart and the appearance of its chambers in the adult cadaver. 441.
Warren, J. J. (and A. M. Weissler, and J. J. Leonard): Modification of ventricular gallop rhythm induced by pooling of blood in the extremities. 502.
Watson, H. (and C. Pickard, K. G. Lowe, and Ian Hill): Selective cine-angiocardiography with image intensification. 459.
Wedgewood, J.: Incomplete rupture of the ascending aorta with secondary aneurysm. 427.
Weissler, A. M. (and J. J. Leonard and J. J. Warren): Modification of ventricular gallop rhythm induced by pooling of blood in the extremities. 502.
Wells, B. G.: Diagnosis of mitral incompetence from left atrial pressure curves. 321.
——: Effect of valvotomy on the murmurs of pulmonary and aortic stenosis. 523.

Willoughby, D. A. (and R. Moulton, and H. G. Spencer): Noradrenaline sensitivity in hypertension measured with a radioactive technique. 224.
Wood, Paul: The vasoconstrictive factor in pulmonary hypertension. 357.
Woolf, C. R. (and W. Paul, and R. W. Gunton): Diagnostic use of an ear oximeter in congenital heart disease. 311.

Z

Zimmerman, Henry (and Jorge Martins de Oliveira, and Mohinder P. Sambhi): Electrocardiogram in pectus excavatum. 495.
Zuska, J. J. (and F. B. Clare, and R. Gorlin): Evidence for pulmonary vasoconstriction in man. 346.

INDEX OF SUBJECTS

A

Abstracts of Cardiology. 150, 294, and 436.
Aconitine-induced cardiac arrhythmia (G. French). 140.
Amyl nitrite in differentiating mitral and aortic systolic murmurs. The use of (J. Barlow and J. Shillingford). 162.
Anatomy of the mitral valve. The functional and clinical (J. C. Van der Spuy). 471.
Aneurysm. Incomplete rupture of the ascending aorta with secondary (J. Wedgewood). 427.
Ankylosing spondylitis. The aortic lesion of (B. M. Ansell, E. G. L. Bywaters, and I. Doniach). 507.
Anti-streptolysin O Titre in rheumatic carditis (E. N. Chamberlain, C. A. St. Hill, and S. Cope). 183.
Aorta with bacterial endarteritic vegetations. Double-barrelled (G. L. Robinson). 571.
Aortic lesion of ankylosing spondylitis (B. M. Ansell, E. G. L. Bywaters, and I. Doniach). 507.
Aortic regurgitation. Ventricular septal defect with pulmonary stenosis and (D. M. Collins, T. East, M. P. Godfrey, P. Harris, and S. Oram). 363.
Aortic stenosis. The effect of valvotomy on the murmurs of pulmonary and (B. G. Wells). 523.
Aortic stenosis. Electrocardiogram in (Zahira H. Abdin). 31.
Aortic systolic murmur developing with increasing age (D. L. Bruns and L. G. Van der Hauwaert). 370.
Aortic systolic murmurs. The use of amyl nitrite in differentiating mitral and (J. Barlow and J. Shillingford). 162.
Aortography. Coronary artery catheterization during thoracic (A. M. Johnson and W. D. Logan). 411.
Arrhythmia. Aconitine-induced cardiac (G. French). 140.
Asymetrical hypertrophy of the heart in young adults. (D. Teare). 1.
Atrial dissociation (Mario Gomes Marques). 335.
Atrial pressure curves. The diagnosis of mitral incompetence from left (B. G. Wells). 321.
Atrial septal defect. Cardiac syncope in (C. Papp). 9.
Atrial septal defect. Vectorcardiogram in (N. A. J. Hamer). 215.
Atrio-ventricular valve. Incompetent congenital bicuspid right (N. Coulshed). 433.
Auscultation in patent ductus arteriosus: with a description of two fistulæ simulating patent ductus (Catherine Neill and P. Mounsey). 61.

B

Blood in the extremities. Modification of ventricular gallop rhythm induced by pooling of (J. J. Leonard, A. M. Weissler, and J. V. Warren). 502.
British Cardiac Society. Proceedings of. 290 and 582.

C

Cadaver. The Orientation of the heart and the appearance of its chambers in the adult (R. Walmsley). 441.
Calcification of the mitral region (E. Linko and E. Sysimetsa). 329.
Calf and foal. Patency of the ductus arteriosus in the newborn (E. C. Amoroso, G. S. Dawes, and Joan C. Mott). 92.
Cardiac infarction. Disappearance of pathological Q waves after (M. P. Pappas). 123.
Cardiac infarction and of heparin therapy on the lipoproteins. The effect of acute (E. M. M. Besterman). 21.
Cardiogram of anterior cardiac infarction. The influence of ventricular hypertrophy upon the (J. F. Goodwin). 191.
Catheterization during thoracic aortography. Coronary artery (A. M. Johnson and W. D. Logan). 411.
Cerebral blood flow in mitral stenosis and its response to carbon dioxide (H. A. Dewar and L. A. G. Davidson). 516.
Cine-angiocardiography with image intensification. Selective (H. Watson, C. Pickard, K. G. Lowe, and Ian Hill). 459.
Circulatory disorders. The role of venous constriction in (János P. Radó, Endre Gonda, and Erwin Kovács). 389.
Circulatory effects of changing position in mitral disease (D. Cardus, J. Mackinnon, and G. Wade). 233.
Clinical and radiological aspects of calcification of the mitral region (E. Linko and E. Sysimetsa). 329.
Coalworkers. The right ventricle and the small pulmonary arteries in (A. J. Thomas and W. R. L. James). 403.
Coarctation of the aorta. A surgical study of (R. Nicks). 351.
Collateral circulation after division of subclavian artery. Unilateral rib-notching from (Maurice Campbell). 253.
Congenital heart disease. The diagnostic use of an ear oximeter in (C. R. Woolf, W. Paul, and R. W. Gunton). 311.
Congenital heart disease. Evaluation of dye injection methods in (W. Falholt and J. Fabricius). 117.
Congenital heart disease. Pulmonary hypertension in (W. Evans and D. S. Short). 529.
Congenital heart disease. Symposium on. 261.
Coronary artery catheterization during thoracic aortography (A. M. Johnson and W. D. Logan). 411.
Coronary heart disease. Hæmodynamic consequences of (Ottar Muller and Karl Rørvik). 302.
Coronary heart disease in the presence of pulmonary disease (A. J. Thomas). 83.
Correlation between various assessments of pulmonary arterial pressure in mitral stenosis (J. F. Boyd, S. D. Scott Park, and George Smith). 466.

D

Diagnostic use of an ear oximeter in congenital heart disease (C. R. Woolf, W. Paul, and R. W. Gunton). 311.
Digitalis and intractable heart failure (E. Fletcher and C. F. Brennan). 204.
Diphtheritic myocarditis. Serum glutamic oxalacetic transaminase levels in (E. Chesler). 244.
Direct left atrial pressure tracings and the degree of mitral obstruction (S. R. McCampbell). 341.
Double-barrelled aorta with bacterial endarteritic vegetations (G. L. Robinson). 571.
Ductus arteriosus in the newborn calf and foal. Patency of the (E. C. Amoroso, G. S. Dawes, and Joan C. Mott). 92.
Dye injection methods in congenital heart disease. Evaluation of (W. Falholt and J. Fabricius). 117.
Dyspnœa. Tracheal vascular ring causing. (N. Coulshed and E. Wyn Jones). 147.

E

Electrocardiogram in aortic stenosis (Zahira H. Abdin). 31.
Electrocardiogram in left ventricular hypertrophy. The orthogonal (E. J. Fischmann). 167.
Electrocardiograms. Observer variation in reports on (L. G. Davies). 153.
Electrocardiogram in pectus excavatum (Jorge Martins de Oliveira, Mohinder P. Sambhi, and Henry Zimmerman). 495.
Electrocardiogram in progressive muscular dystrophy (G. W. Manning and G. J. Cropp). 416.
Electrocardiogram in pulmonary embolism (R. H. Cutforth and S. Oram). 31.
Electrocardiograms with short P–R interval and aberrant QRS complex (L. M. Sanghvi and S. M. Misra). 357.
Electrocardiogram in syphilitic heart disease (G. Storey). 483.
Electrocardiographic diagnosis of right ventricular hypertrophy in infancy and childhood (A. Hollman). 129.
Emanuel, J. G. 579.
Estimating mitral regurgitation by dye dilution curves. Simple method for (J. Shillingford). 229.

F

Fibrinolysis in myocardial infarction (R. Hume). 15.
Fœtal paroxysmal auricular tachycardia (C. W. Kesson). 552.

G

Gallavardin, Louis. 299.

H

Hæmodynamic consequences of coronary heart disease (O. Muller and K. Rørvik). 302.
Heart: 1909–1958. 297.
Heart and the appearance of its chambers in the adult cadaver. The orientation of the (R. Walmsley). 441.
Heart failure. Digitalis and intractable (E. Fletcher and C. F. Brennan). 204.
Heparin therapy on the lipoproteins. The effects of acute cardiac infarction and of (E. M. M. Besterman). 21.
Hypertension measured with a radioactive sodium technique. Noradrenaline sensitivity in (R. Moulton, H. G. Spencer, and D. A. Willoughby). 224.
Hypertension. Pulmonary function in pulmonary (M. B. McIlroy and G. H. Apthorp). 397.
Hypertension. Thoracolumbar sympathectomy in (W. E. Parkes). 249.
Hypertrophy upon the cardiogram of anterior cardiac infarction. The influence of ventricular (J. F. Goodwin). 191.
Hypertrophy of the heart in young adults. Asymetrical (D. Teare). 1.
Hypertrophy in infancy and childhood. Electrocardiographic diagnosis of right ventricular (A. Hollman). 129.
Hypertrophy. The orthogonal electrocardiogram in left ventricular (E. J. Fischmann). 167.
Hypothermia. The spatial vectorcardiogram in (D. Emslie-Smith). 175.

I

Incompetent congenital bicuspid right atrio-ventricular valve (N. Coulshed). 433.
Influence of ventricular hypertrophy upon the cardiogram of anterior cardiac infarction (J. F. Goodwin). 191.

L

Lipoproteins. The effect of acute cardiac infarction and of heparin therapy on the (E. M. M. Besterman). 31.
Lung volume in mitral disease. Residual (R. Garbagni, P. G. Angelino, A. Brusca, and E. Minetto). 479.

M

Marfan's syndrome. Supra-aortic stenosis associated with (A. F. Burry). 143.
Mitral and aortic systolic murmurs. The use of amyl nitrite in differentiating (J. Barlow and J. Shillingford). 162.
Mitral disease. Circulatory effects of changing position in (D. Cardus, J. Mackinnon, and G. Wade). 233.
Mitral disease. Residual lung volume in (R. Garbagni, P. F. Angelino, A. Brusca, and E. Minetto). 479.
Mitral incompetence from left atrial pressure curves. The diagnosis of (B. G. Wells). 321.
Mitral obstruction. Direct left atrial pressure tracings and the degree of (S. R. McCampbell). 341.
Mitral region. Clinical and radiological aspects of calcification of the (E. Linko and E. Sysimetsa). 329.
Mitral regurgitation by dye dilution curves. Simple method for estimating (J. Shillingford). 229.
Mitral stenosis. Correlation between various assessments of pulmonary arterial pressure in (J. F. Boyd, S. D. Scott Park, and George Smith). 466.

Mitral stenosis. Patent ductus arteriosus with (J. Mackinnon and R. M. Briggs). 424.
Mitral stenosis and its response to carbon dioxide. Cerebral blood flow in (H. A. Dewar and L. A. G. Davidson). 516.
Mitral valve. The functional and clinical anatomy of the (J. Van der Spuy). 471.
Mitral valve. Restenosis of the (J. R. Belcher). 76.
Muscular dystrophy. The electrocardiogram in progressive (G. W. Manning and G. J. Cropp). 416.
Myocardial infarction. Fibrinolysis in (R. Hume). 15.
Myxoma of the left auricle with direct pressure tracings (J. R. H. Towers and C. P. Newcombe). 575.

N

National Heart Hospital (1857–1957). 137.
Natural history of ventricular septal defect. (L. Brotmacher and Maurice Campbell). 97.
Noradrenaline sensitivity in hypertension measured with a radioactive sodium technique (R. Moulton, H. G. Spencer and D. A. Willoughby). 224.

O

Orientation of the heart and the appearance of its chambers in the adult cadaver (R. Walmsley). 441.
Orthogonal electrocardiogram in left ventricular hypertrophy (E. J. Fischmann). 167.
Oximeter in congenital heart disease. Diagnostic use of an ear (C. R. Woolf, W. Paul, and R. W. Gunton). 311.

P

Paroxysmal tachycardia. Fœtal (C. W. Kesson). 552.
Patency of the ductus arteriosus in the newborn calf and foal (E. C. Amoroso, G. S. Dawes, and Joan C. Mott). 92.
Patent ductus arteriosus: with a description of two fistulæ simulating patent ductus. Auscultation in (Catherine Neill and Patrick Mounsey). 61.
Patent ductus arteriosus with mitral stenosis (J. Mackinnon and R. M. Briggs). 424.
Patent ductus arteriosus with ventricular septal defect (G. L. Higgins). 421.
Pectus excavatum. Electrocardiogram in (Jorge Martins de Oliveira, Mohinder P. Sambhi, and Henry Zimmerman). 495.
Pressure tracings and the degree of mitral obstruction. Direct left atrial (S. R. McCampbell). 341.
P–R interval and aberrant QRS complex. Electrocardiograms with short (L. M. Sanghvi and S. N. Misra). 357.
Proceedings of the British Cardiac Society. 290 and 582.
Pulmonary and aortic stenosis. Effects of valvotomy on the murmurs of (B. G. Wells). 523.
Pulmonary arteries in coalworkers. The right ventricle and the small (A. J. Thomas and W. R. L. James). 403.
Pulmonary arterial pressure in mitral stenosis. Correlation between various assessments of (J. F. Boyd, S. D. Scott Park, and George Smith). 466.
Pulmonary disease. Coronary heart disease in the presence of (A. J. Thomas). 83.
Pulmonary embolism. Electrocardiogram in (R. H. Cutforth and S. Oram). 31.
Pulmonary function in pulmonary hypertension (M. B. McIlroy and G. H. Apthorp). 397.
Pulmonary hypertension in congenital heart disease (W. Evans and D. S. Short). 529.
Pulmonary hypertension. Vasoconstrictive factor in (P. Wood). 557.
Pulmonary stenosis and aortic regurgitation. Ventricular septal defect (D. M. Collins, T. East, M. P. Godfrey, P. Harris, and S. Oram). 363.
Pulmonary stenosis. Ventricular septal defect with (L. Brotmacher and Maurice Campbell). 379.
Pulmonary vasoconstriction in man. Evidence for (R. Gorling, F. B. Clare, and J. J. Zuska). 346.

Q

QRS complex. Electrocardiograms with short P–R interval and aberrant (L. M. Sanghvi and S. N. Misra). 357
Q waves after cardiac infarction. Disappearance of pathological (M. P. Pappas). 123.

R

Radio-active sodium technique. Noradrenaline sensitivity in hypertension measured with a (R. Moulton, H. G. Spencer, and D. A. Willoughby). 224.
Reports on electrocardiograms. Observer variation in (L. G. Davies). 123.
Restenosis of the mitral valve (J. R. Belcher). 76.
Rheumatic carditis. Anti-streptolysin O titre in rheumatic carditis (E. N. Chamberlain, C. A. St. Hill, and S. Cope). 183.
Rupture of the ascending aorta with secondary aneurysm. Incomplete (J. Wedgewood). 427.

S

Serum glutamic oxalacetic transaminase levels in diphtheritic myocarditis (E. Chesler). 244.
Spatial vectorcardiogram in hypothermia (D. Emslie-Smith). 175.
Subclavian artery. Unilateral rib-notching from the collateral circulation after division of the (Maurice Campbell). 253.
Supra-aortic stenosis associated with Marfan's syndrome (A. F. Burry). 143.
Surgical study of coarctation of the aorta (R. Nicks). 351.
Sympathectomy in hypertension. Thoracolumbar (W. E. Parkes). 249.
Symposium on congenital heart disease. 261.

Syncope in atrial septal defect. Cardiac (C. Papp). 9.
Syphilitic heart disease. The electrocardiogram in (G. Storey). 483.
Systolic murmur developing with increasing age. The aortic (D. L. Bruns and L. G. Van der Hauwaert). 370.

T

Tracheal vascular ring causing dyspnœa (N. Coulshed and E. Wyn Jones). 147.

U

Unilateral rib-notching from the collateral circulation after division of the subclavian artery (Maurice Campbell) 253.

V

Valvotomy on the murmurs of pulmonary and aortic stenosis. The effect of (B. G. Wells). 523.
Vasoconstriction in man. Evidence for pulmonary (R. Gorling, F. B. Clare, and J. J. Zuska). 346.
Vasoconstrictive factor in pulmonary hypertension (P. Wood). 357.
Vectorcardiogram in atrial septal defect (N. A. J. Hamer). 215.
Vectorcardiogram in hypothermia. The spatial (D. Emslie-Smith). 175.
Venous constriction in circulatory disorders. The role of (János P. Radó, Endre Gonda, and Erwin Kovács). 389.
Ventricle and the small pulmonary arteries in coalworkers. The right (A. J. Thomas and W. R. L. James). 403.
Ventricular gallop rhythm induced by pooling of blood in the extremities. Modification of (J. J. Leonard and J. V. Warren). 502.
Ventricular septal defect. The natural history of (L. Brotmacher and M. Campbell). 97.
Ventricular septal defect. Patent ductus arteriosus with (G. L. Higgins). 421.
Ventricular septal defect with pulmonary stenosis (L. Brotmacher and Maurice Campbell). 379.
Ventricular septal defect with pulmonary stenosis and aortic regurgitation (D. M. Collins, T. East, M. P. Godfrey, P. Harris, and S. Oram). 363.

rt). 370.

ce Campbell)

ovács). 389.
nes). 403.
ard and J. V.

. P. Godfrey,